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INTUBATED URETEROTOMY

A New Operation for Ureteral and Ureteropelvic Stricture

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THE surgery of the ureter has lagged behind the surgery of the kidney in a manner that is difficult, now, to explain. Only a few years ago there was a general feeling that the ureter seldom required attention, except for the occasional case in which it had to be removed. This belief perhaps arose from the fact that, after pyelography was invented, the medium was always injected through a catheter lying in the renal pelvis. Pyelography brought about a rapid increase in our knowledge concerning renal pathology, much of it concerning the effects of obstruction. In conservative kidney surgery, attention centered upon plastic operations on the pelvis, with the result that the consideration, which now seems obvious, namely, that the cause of the pelvic dilatation must be an obstruction lying at some point in the ureter, was ignored. Next, ureteropelvic obstructions were treated by means of plastic operations, and much argument arose as to the desirability of using a tube splint after such operations.

Hunner's persistent campaign brought the realization that there are many ureteral obstructions below the ureteropelvic junction, and that many of these are amenable to treatment by dilatation. The operative treatment of strictures not responding to dilatation has remained unsatisfactory; in fact, it is seldom attempted.

About 10 years ago, when faced with a dense, fibrous, thick walled stricture of the upper ureter, I applied the principle of the Rammstedt operation for pyloric stenosis, and divided the stricture longitudinally, passing through all the layers of the ureteral wall except the mucosa (Fig. 1). The result was most satisfactory. Good results have since been obtained with this technique by Bidgood and Roberts, Gibson and others, and the operation is now generally adopted for the comparatively few cases in which the method is applicable.

The question of splinting after ureteropelvic plastic operations came up every time such an operation had to be done. Opinions have varied radically as to the value of the splint. Peck, Harris, Cabot, Moore, Sargent, Priestley, and Ormond have all favored splinting. Gibson puts the case for splinting as follows: "No matter how generous the surgeon is in the use of sutures in plastic repair, the outcome is likely to be a failure unless he makes use of splinting; conversely, if he places his dependence on adequate splinting the result will almost certainly be successful even though he uses no sutures at all." In spite of this, Gibson states that he does not "eschew the use of sutures entirely."

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In quoting authorities for the use of the ureteral splint, it should not be forgotten that Albarran recommended that whenever the kidney is opened, as large a ureteral catheter as possible should be passed down the ureter and left in place for several days.

It seemed to me that the results were better in the splinted cases, but splint or no splint, there were all too many failures, partial or complete.

Another aspect of the problem appeared as the result of experiences with urethral strictures. I had occasion, nearly 20 years ago, to operate upon a patient with a very severe bulbomembranous stricture, accompanied by extensive perineal scarring and multiple fistulous tracts. After the scarred, diseased tissue was laboriously dissected away, there was left a huge hole in the perineum, and a narrow ribbon of urethral wall, representing a part of the roof of that organ, bridging a gap in the urethra a good inch and a quarter long. I lacked the courage to extend the dissection far enough to permit the freeing of the urethra, freshening of its ends, and circular suture in the classic manner. Instead, I passed a No. 24 F. catheter through the entire length of the urethra into the bladder, fastened it in place, and left the wound unsutured. The catheter was visible at the bottom of the cavity for many days, but after 2 weeks it was covered by healthy granulations. At the end of 3 weeks it was withdrawn, and the result was so excellent that no later dilatations were required. Evidently, the epithelium had grown around the circumference of the catheter, and a new urethra, healthy and pliable, was created. Welland Howard has since described a similar procedure in which, if necessary, he even splits the urethra into several ribbons to permit the passage of the catheter.

In June, 1940, I was confronted by a narrow, thin-walled stricture of the upper ureter just at the point where the ureter disappeared into a kidney with a completely intrarenal pelvis (Fig. 2, a). The absence of an extrarenal pelvis removed any possibility of using any of the usual plastic operations. The Rammstedt type of operation was out of the question, as the wall of the ureter at the site of the stricture seemed even thinner than the wall of the normal portion of the ureter. At a loss to know what to do, I finally decided to apply the same principle used so successfully in urethral strictures, that is, to introduce a tube splint which was to remain in place for 2 or 3 weeks. A description of this case follows:

CASE 1. Mr. D. B., aged 16 years. In spite of attacks of mastoiditis, sinusitis, and rheumatic fever, this patient had usually enjoyed good health. In March, 1940, there was an attack of pain in the right kidney region. This pain recurred fairly frequently, often accompanied by hematuria. There was no frequency.

Roentgenograms taken June 12, 1940, showed a small stone in a lower calyx of the right kidney and a persistent narrowing of the uppermost part of the right ureter (Fig. 3, a). On June 14, 1940, a No. 12 F. bulb was passed to the right kidney, meeting moderate resistance. After this, two or three more attacks of pain, with hematuria, occurred, and roentgenograms showed the stone to be in the pelvis proper. It was felt that the narrowing seen in the urogram must represent an obstruction, otherwise this small stone would have become engaged in the ureter.

Operation was performed August 2, 1940. The kidney was easily exposed and freed. The ureter was brought up on a tape. The upper portion of it was markedly adherent and dissected with difficulty until a firm fibrous capsule was split longitudinally. Within this was found a perfect ureter. The pelvis was entirely intrarenal with only a very slight widening at the hilus. The main artery entered the hilus around the side of the ureter. About 15 millimeters below the kidney there was a sharp narrowing of the ureter, evidently congenital, as the wall was no thicker than normal and there was no evidence of any inflammatory change in the wall. A small artery joined the ureter at this point. It was doubly ligated and divided. A considerable portion of the fibrous capsule was cut away. Ureterotomy was made all the way up to the kidney but the hilus would not admit even the little finger. Probes and forceps of all kinds were used to explore the kidney but the stone could not be located. A roentgenogram was made on the table and a nephrotomy was made over the stone shadow as nearly as could be made out. In spite of this, the stone could not be found, and further efforts were abandoned in order to avoid damage to the kidney. The ureteral incision was extended down through the stricture. A Rammstedt operation could not be done as the ureteral wall was everywhere of normal thickness. A No. 12 rubber catheter was brought down through the nephrotomy into the ureter. The ureter was closed loosely about it with a suture of No. 000 plain catgut, but a considerable defect remained at the point of the stricture (Fig. 2, c, d). It was decided to leave the tube in place at least 2 weeks in the hope that the ureter would grow around it, thus relieving the stricture

and making it possible for the stone to pass should it again become free in the pelvis.

There was some wound infection, with fever. The tube was removed on the 14th day, and 48 hours later all urinary drainage had ceased. He left the hospital on the 27th day.

On October 17, 1940, the patient felt very well and had had no more attacks. The urine contained a few pus cells and some staphylococci. On October 24, 1940, intravenous urogram showed a small stone shadow, apparently in a calyx or in the parenchyma. The upper ureter was well shown and was uniform in diameter, the persistent narrowing formerly seen being entirely obliterated (Fig. 3 b). On August 23, 1942, the patient reported by letter that he was in perfect health, engaging in very heavy physical labor, as well as in active social life, and had never had the slightest recurrence of pain in the kidney.

The excellent result obtained encouraged me to follow the same plan in another similar case.

CASE 2. Mrs. A. K., aged 46 years. Pain in the left kidney began in 1917. Calculous pyonephrosis was found in 1925, and the left kidney was removed. For one year before admission, there were occasional pain in the right back, slight burning on urination, dizziness, and nervousness, but no frequency of urination. There was pyuria, and x-ray examination showed a stone shadow in the right kidney region.

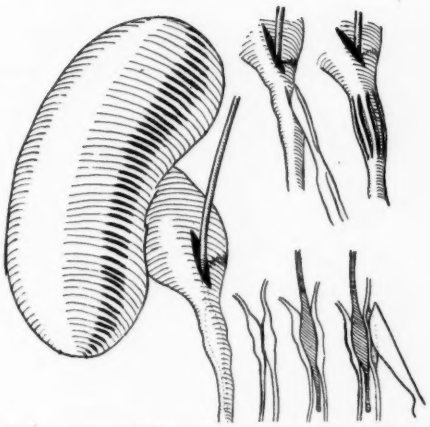

Fig. 1. Rammstedt type operation for thick-walled ureteral stricture. The stricture is stretched by a bougie inserted through a pyelotomy incision; one or more longitudinal incisions are made passing through all layers of the ureteral wall except the mucosa.

The urine contained many bacilli. Phenolsulfonphthalein test returned 18 per cent in one-half hour. Pyelography showed an abnormal, irregular, but not particularly dilated pelvis in a large kidney shadow, and a normal ureter. The stone extended to the ureteropelvic junction.

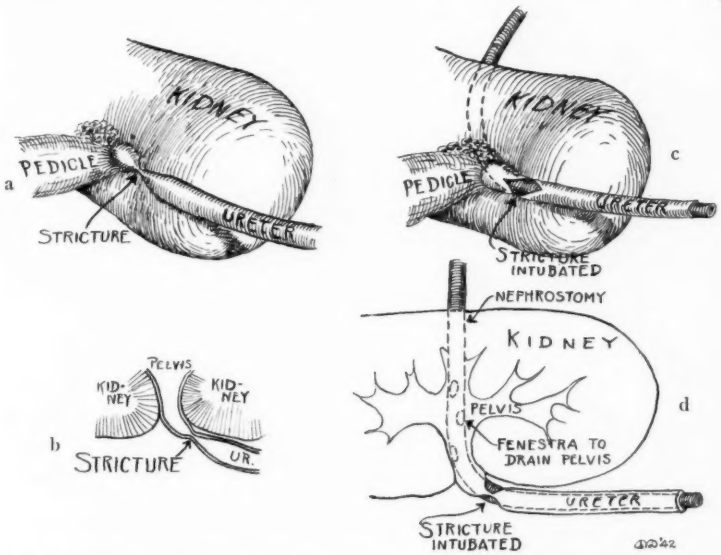

Fig. 2. Case 1. a, Conditions as found at operation; b, diagrammatic section through ureter as it entered kidney; c, stricture incised, splint tube in place in ureter, proximal end brought out through nephrotomy incision; d, diagrammatic section showing conditions at end of operation.

Fig. 3. Case 1. a, left, Intravenous urogram, before operation, showing stricture of upper ureter. b, Intravenous urogram, 3 months after operation, showing stricture no longer present.

On May 21, 1940, operation was performed. The upper ureter was encased in a thick mass of indurated fat. The pelvis was entirely intrarenal, but the stone fortunately could be removed through a long ureterotomy. The ureter was definitely narrowed below the kidney. A rubber tube, about No. 14 F. in size, and equipped with many fenestra, was passed down the ureter 10 or 12 centimeters, and brought out through a small nephrotomy incision (same as Case 1). No ureteral sutures were used, and the tube was exposed in the open ureterotomy.

The tube was accidentally pulled out on the 10th postoperative day, and there was practically no urinary drainage afterward. The wound healed *per primam*. The patient was out of bed on the 14th day and left the hospital on the 18th day.

A month later 36 per cent of phenolsulfonphthalein was excreted in one-half hour, and the patient felt perfectly well. Two months later the ureter was dilated with a No. 10 F. bulb. The urine was clear and contained no pus, blood, or bacteria. Later, the ureter was dilated twice, to sizes No. 12 F. and No. 14 F. On July 2, 1942, the patient felt perfectly well, and the urine was clear and uninfected. No postoperative pyelogram has been taken.

Not long afterward a third case presented itself. The situation differed somewhat in that there was a good-sized extrarenal pelvis, and the stricture was considerably longer.

Case 3. Mrs. B. P., aged 28 years. This patient had been troubled with marked pain in her right side since the birth of her first child. Investigations in the hospital showed that the left kidney and ureter were normal, the right kidney pelvis moderately but definitely dilated with a persistent marked narrowing just below the ureteropelvic junction, suggesting an aberrant blood vessel. The ureter below this point was also slightly dilated, suggesting another slight stricture at the lower end (Fig. 4).

Operation was performed November 19, 1941. The external appearance of the kidney was perfectly normal and it was not adherent, and was freed very easily. The ureter below the kidney appeared perfectly normal. It was brought up on a tape and dissection was then carried upward, thus disclosing a marked stenotic area about 1¼ centimeters in length just below the ureteropelvic junction. There was no aberrant artery. Above this point the extrarenal pelvis was markedly distended even when the ureter below was quite empty (Fig. 5, a). All of the adventitial tissue and blood vessels were dissected away from the stenotic area very carefully. It was found that there were two layers of fibrous tissue completely surrounding the pelvis, and these were divided and stripped away. Pyelotomy was then made, and the urine spurted out under considerable pressure. The edges of this incision were held up with fine black silk traction sutures. A No. 12 bulb could just be forced through the area of stenosis disclosing the fact that its walls were very thin, even thinner than those of the normal portion of the ureter. A No. 14 bulb could not be passed through the stricture. With the No. 14 bulb held in place, the ureter was incised longitudinally until the bulb passed freely down into the lower ureter. A small rubber tube about size No. 14 F. was then prepared by cutting the end obliquely, and it was passed down through the pyelotomy into the ureter to a point about 3.5 centimeters below the incision in the ureter. A considerable area of this tube was exposed at the site of the incision. Three fenestra were then cut in this tube so that they would lie in the pelvis. The pyelotomy was drawn together over the tube with 1 suture of No. 000 plain catgut, but no sutures were used in the ureterotomy (Fig. 5 b, c). The tube was brought out through the upper angle of the incision. The kidney, which was moderately movable, was fastened up to the muscles around the 12th rib with one capsular suture of No. 2 chromic catgut. The ureter was then seen to lie straight in a normal position.

The patient did very well. The incision healed *per primam* around the tube. The tube remained in place 15 days, draining considerable quantities of urine. On the 13th day it was clamped and remained clamped for 24 hours with no leakage about it. There was very slight discomfort at first but this quickly disappeared. On the 15th day under the fluoroscope, 12½ per cent skiodan solution was injected through the tube. It filled the pelvis quickly, outlined the ureter below the pelvis, and entered the bladder. A film was exposed. The tube was then withdrawn under observation by the fluoroscope. One could easily see the upper ureter and it had at least the same diameter as that below. Another film was immediately exposed. Following the removal of

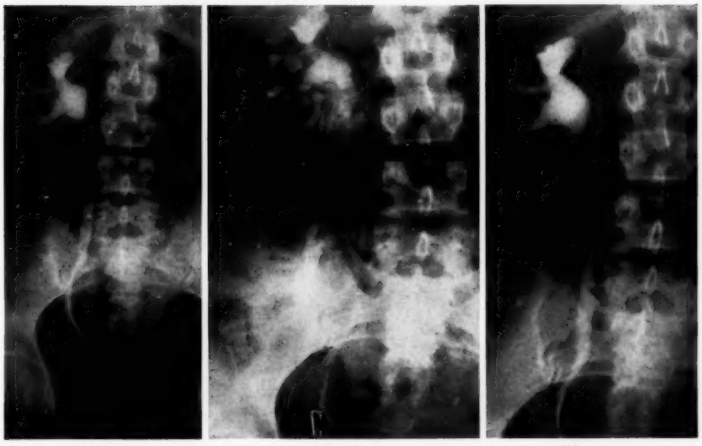

Fig. 4. Fig. 6. Fig. 7.

Fig. 4. Case 3. Retrograde pyeloureterogram, before operation, showing marked ureteropelvic stricture.

Fig. 6. Case 3. Film made immediately after withdrawing tube. Arrow points to ureteral shadow of wide diameter at site of former stricture.

Fig. 7. Case 3. Retrograde pyeloureterogram 6 months after operation; stricture no longer present.

the tube, no urine leaked through the incision, and the patient had no discomfort.

Study of the x-ray films showed that immediately after the removal of the tube, the part of the ureter formerly strictured was very well outlined and retained the diameter of the tube at all points (Fig. 6).

The patient's pain was entirely relieved. The urine remained clear and uninfected. The lower ureter was dilated on several occasions. On May 18, 1942, the retrograde pyeloureterogram shown in Figure 7 was taken, proving that the ureteral stenosis had been completely eliminated. At present the patient is perfectly well.

In the fourth case an upper ureteral stricture was complicated by a membranous valve at the ureteropelvic junction. The operative method was now employed with great confidence as to the outcome.

Case 4. Mrs. G. I., aged 23 years. This patient had always been underweight, but enjoyed fairly good health until her first child was born 2½ years ago. She then developed what was diagnosed as postpartum pyelitis, which persisted. Symptoms of frequency and burning recurred from time to time, and there was usually a slight afternoon fever. She was examined by Dr. George M. Laws. The infecting organism was Escherichia coli communis. Indigocarmine appeared in 8 minutes from the right kidney, and did not appear in 15 minutes from the right. Retrograde pyelograms showed no evidence of obstruction on the right side, but a moderate hydronephrosis on the left, with an essentially normal

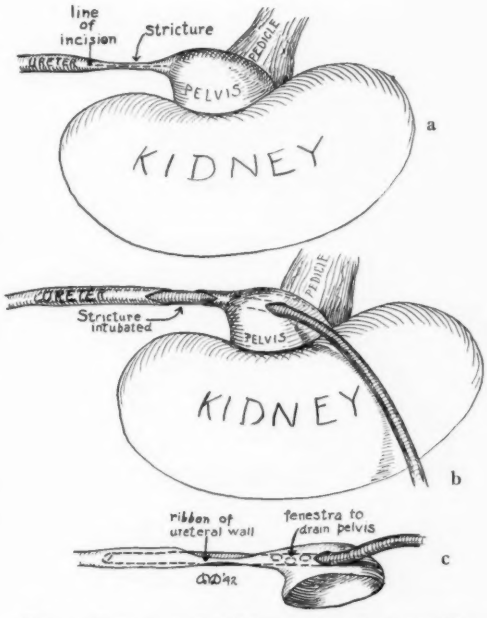

Fig. 5. Case 3. a, Conditions as found at operation. The stricture is actually a little below the ureteropelvic junction; b, stricture incised, splint tube in place, proximal end brought out through pyelotomy incision; c, diagrammatic representation of conditions at end of operation.

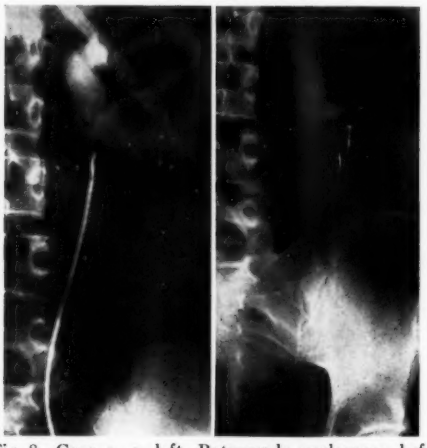

Fig. 8. Case 4. a, left, Retrograde pyelogram, before operation, with catheter partly withdrawn, showing normal ureter and ureteropelvic narrowing. b, Intravenous urogram, before operation. Film taken at 1 hour and 45 minutes, showing retention in pelvis.

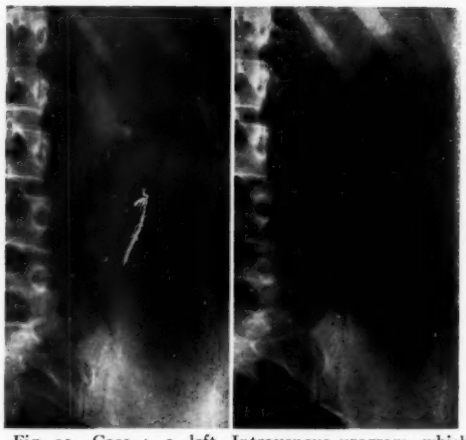

Fig. 10. Case 4. a, left, Intravenous urogram, which was taken 2½ months after operation. Film made at 15 minutes, showing excellent filling of pelvis. b, In this film made at 1 hour, the pelvis is shown to be practically empty.

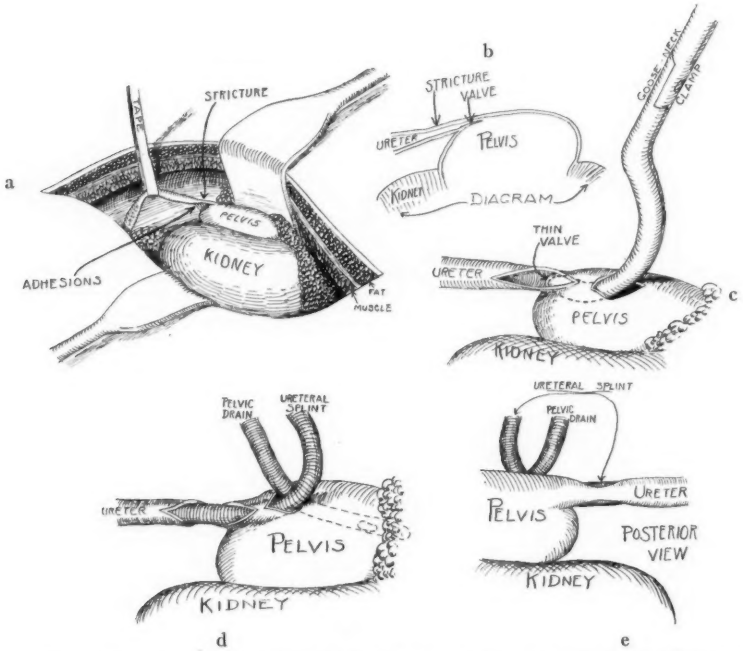

Fig. 9. Case 4. a, Conditions as found at operation; b, diagrammatic section of ureter and pelvis, showing stricture and valve; c, valve pushed down into ureter by tip of clamp; d, stricture incised, valve removed, splint tube in place, with proximal end brought out through pyelotomy incision, separate drainage tube in pelvis; e, posterior view at end of operation, showing ribbon of ureteral wall along splint tube.

Fig. 11.

Fig. 13.

Fig. 14.

Fig. 11. Case 5. Retrograde pyeloureterogram, before operation, showing left hydronephrosis, ureter narrow and thread-like in its upper third, lower two-thirds normal. Note large stones in right kidney.

Fig. 13. Case 5. Pyelogram made by injecting through tube. Note outlines of new formed ureter alongside tube.

Fig. 14. Case 5. Intravenous urogram made 6 months after operation. Note widely patent ureter, compare with Figure 11.

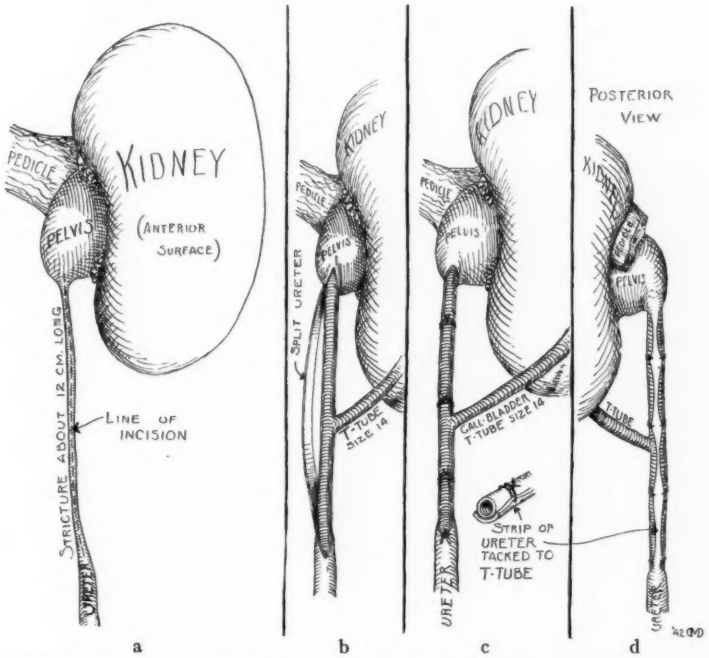

Fig. 12. Case 5. a, Conditions as found at operation; b, stricture incised through its entire length, T-tube in place. Note that ureteral ribbon does not stay in contact with tube; c, ureteral ribbon held to T-tube by sutures; d, posterior view, showing ureteral ribbon closely applied to T-tube. Stem of T-tube provides urinary drainage.

Fig. 15. Case of Dr. Edward L. Keyes. Intravenous urogram made 13 years after operation. Note widely patent upper ureter.

ureter, suggesting ureteropelvic obstruction (Fig. 8, a). Intravenous urography showed a similar picture, with the right pelvis empty after 30 minutes, the left pelvis appearing later than the right and still well filled at 1 hour and 45 minutes (Fig. 8, b). Treatment with sulfonamides brought about only a temporary clearing of the urine. The slight fever was so persistent that the patient feared she had tuberculosis and consulted Dr. Burgess Gordon. I saw her November 14, 1941 at the request of Dr. Gordon and Dr. Lewis B. Scheffey. Dr. Laws very courteously made his records and x-ray films available. On November 28, 1941 cystoscopy showed the bladder, ureteral orifices, and urethra normal. Urine from the right kidney showed no pus or bacteria, that from the left side a moderate number of pus cells and numerous clumps of bacilli. Phenolsulfonphthalein test: Appearance time, right 4 minutes, left 4½ minutes; collection time 10 minutes; right 14 per cent; left 4½ per cent; transvesical, trace. It was felt that the condition of the left kidney was sure to grow progressively worse, and operation, with the view of relieving the obstruction and saving the kidney, was advised.

Operation was performed December 16, 1941. The lower pole of the kidney was easily freed. The ureter was then brought up on a tape and seemed to have a normal appearance. Dissection was then carried carefully up the ureter. There was a small vein in the periureteral fat running to the renal capsule in the lower pole, but this was entirely a capsular vessel and there was no artery accompanying it. It was ligated and divided with no effect on the kidney. It was then possible to expose the pelvis very completely without exposing the upper half of the kidney. Just below the ureteropelvic junction, the ureter narrowed to less than half its diameter elsewhere. There were bands of adhesions joining this part of the ureter to the pelvis, and the lower portion of the pelvis was rounded and projected a little below the ureteropelvic junction (Fig. 9, a, b). A small pyelotomy was then made and a gooseneck clamp was inserted. In spite of extensive probing, it would not enter the ureter but always pushed out the lower portion of the pelvis. The ureter was therefore incised, beginning at the point where the narrowing began. The incision was carried upward until one could see within the ureter the tip of the gooseneck clamp covered by a thin membrane, evidently a congenital valve (Fig. 9, c). This was seized with forceps and excised with scissors. The clamp then passed freely down into the ureter. The incision was carried up a little way on the pelvis to insure a widely open ureteropelvic junction. A rubber tube about size No. 14 F., not fenestrated, was then passed through the pyelotomy down the ureter to a distance of about 5 centimeters below the ureterotomy. At the site of the ureterotomy, the ureteral wall now covered only about one-third of the circumference of the tube. No sutures were used. A No. 16 rubber catheter with the end cut off was then passed through the pyelotomy to drain the pelvis (Fig. 9, d, e). The kidney was replaced in position and the tubes were arranged so that the ureter followed a normal course.

The convalescence was excellent and the incision healed *per primam*. On the 14th day there was a transitory episode of fever. On the 16th day, acriflavine solution was injected through the ureteral tube and immediately appeared in the bladder urine. The tube was then withdrawn. A short time later mercurochrome solution was injected through the pelvic tube and it was withdrawn. The next passage of urine was highly colored with mercurochrome. There was never any leakage of urine through the drainage tract. The patient left the hospital on the 22nd day.

On February 2, 1942, and March 2, 1942, catheterized specimens of urine showed no pus or bacteria. The temperature remained normal. An intravenous urogram was made on March 2, 1942. The outline of the left kidney pelvis was much the same as before, but it was well filled at 5 minutes (Fig. 10, a), and completely empty at 30 minutes (Fig. 10, b), whereas before the operation it had been still fully outlined at 1 hour and 45 minutes. Unfortunately, the ureter was not outlined in any of the films. In July, 1942, the patient stated that she had gained 15 pounds in weight and that she felt perfectly well, as she had not for 9 or 10 years before the operation.

The fifth case was remarkable for the extreme length of the stricture. In spite of previous successes, the operative method was used with some misgivings because of the length of the stricture and especially because

the opposite kidney was severely and irreparably damaged. Nevertheless, there appeared to be no other method of dealing with the situation, which I thought then and still think provided an acid test for the procedure.

CASE 5. Mrs. A. B., aged 32 years. Severe pain in the right side began April 15, 1941. Attacks recurred about every 2 weeks, and were accompanied by chills, fever, frequency, and hematuria. Urine was cloudy at all times.

X-ray examination showed multiple large stones in the right kidney region. The urine showed many white blood cells, few red blood cells, and many bacilli.

Cystoscopy was done March 5, 1942. Urine from left kidney was clear, with no bacteria. Phenolsulfonphthalein given intravenously revealed: right, 7 per cent, left 22 per cent in 10 minutes. Left pyeloureterogram showed a marked hydronephrosis; the ureteropelvic junction was funnel-shaped, but the upper ureter very small for 10 centimeters (Fig. 11). The catheter met resistance in this region.

The patient became very ill, developing severe pain in the left kidney region, accompanied by chills, sweats and high fever, indicating that infection of the left kidney had occurred. This infection persisted unabated for 8 days, in spite of large doses of sulfathiazole, and it became apparent that something radical would have to be done to save the patient's left kidney, her only good one.

Operation was performed March 13, 1942. The perirenal fat was adherent and vascular. The ureter was small but thick walled with a thicker capsule than normal and numerous good sized veins coursing along it. It resembled a normal vas deferens. About 10 or 12 centimeters below the kidney it assumed a normal appearance (Fig. 12, a). The extrarenal pelvis was of moderate size and thickened (muscular hypertrophy). Ureterotomy was made in the middle of the narrowed portion. A No. 10 ureteral bulb passed upward to the kidney with great difficulty, and downward with almost equal difficulty, until it reached the normal portion of the ureter. It then went easily to the bladder. Efforts to dilate the ureter further were unsuccessful. When sufficient force was applied, the ureter split. It was felt that relief of the obstruction was absolutely necessary to the patient's welfare, as the other kidney would undoubtedly have to be removed. For this reason, the ureter was boldly incised throughout the entire length of the narrowed portion (10 to 12 cm.). This converted this portion of the ureter into a narrow ribbon. The incision was extended upward a little way into the pelvis. One end of the cross piece of a No. 16 latex gall-bladder T-tube was then inserted in the pelvis. The other end barely reached the lower extremity of the ureteral incision, and was inserted into the normal part of the ureter, and held there by a suture of No. 000 plain catgut (Fig. 12, b). The ribbon of ureteral wall was then held in close approximation to the tube by 3 sutures of No. 000 plain catgut. It did not cover more than one-third the circumference of the tube (Fig. 12, c, d). The stem of the T-tube was brought out the upper angle of the wound for urinary drainage. The wound was closed in the usual manner, with 2 or 3 rubber tissue drains.

Convalescence was afebrile and uneventful. The wound healed by first intention.

On April 14, 1942, skiodan solution was injected through the tube and the x-ray picture shown in Figure 13 was obtained. The lower limb of the T-tube was evidently occluded, but the solution flowed freely around the tube into the bladder. The tube was therefore withdrawn on April 12, 1942, 31 days after the operation. No urine drained through the incision, but the temperature rose to 100 degrees and the patient had pain in the left kidney. A No. 9 ureteral catheter was passed easily to the kidney and left in place 5 days; when it was withdrawn. There were no further symptoms, and the temperature remained normal.

On April 24, 1942, a No. 14 bulb passed to the left kidney with perfect ease, meeting no resistance at any point. The patient left the hospital April 26, 1942. Later she re-entered the hospital, and on May 19, 1942 the right kidney was removed. It was a useless, thin walled sac and contained several large stones. The convalescence was uneventful, and the patient left the hospital June 3, 1942. On July 1, 1942, the patient reported for observation. She felt perfectly well. The catheterized urine was clear, and contained no pus, blood, or bacteria. Phenolsulfonphthalein given intravenously revealed 47 per cent in 30 minutes. On August 17, 1942, a No. 14 bulb again passed to the left kidney with perfect ease. On September 9, 1942, intravenous urography was carried out. The ureter was well outlined, as shown in Figure 14, and obviously of normal diameter or greater. These findings prove beyond doubt that the new ureter is functioning in a thoroughly satisfactory way.

I was unable to find a description of any similar method for treating ureteral strictures until I found, in the 1928 edition of Keyes' *Urology*[1] a recommendation for "intubation of the ureter" in such situations. Since few details were given, I consulted Dr. Edward L. Keyes personally. He gave me full particulars of a patient he had operated upon in 1915. This case is of sufficient interest to quote in full:

"An able-bodied Irish laborer, whose previous history contained nothing relating to his urinary organs, sat for 2 hours on a board covered with ice in February, 1915. Within a few hours he had a severe pain in his left loin, and the next day did not urinate. Alarmed at this, he consulted a physician,

[1] P. 461.

who passed a catheter but obtained no urine. Meanwhile the pain had disappeared and the patient felt perfectly well. So for six days he did nothing, though during that time he passed not a single drop of urine. He then entered St. Vincent's Hospital.

"He said he felt well but he was mentally a little stupid, his superficial capillaries a little congested, his intestines distended, his blood pressure 170, his temperature normal, his left loin slightly tender, but owing to distention the kidney could not be felt.

"The roentgen rays showed a large left kidney but no stone. The cystoscope showed a congestion of the bladder vessels corresponding to the skin congestion. There was not a drop of urine in the bladder. The ureter catheter went up 30 cm. of the left ureter, but drew no urine. A filiform ureteral bougie entered the right ureter for only 5 cm. and drew no urine.

"I therefore immediately cut down upon the right loin but found no kidney there. I turned him over and opened the left loin and found the left kidney very large, congested and tense. I incised the cortex and pushed a tube into the pelvis of the kidney, liberating an ounce or more of urine.

"For two days he was semicomatose and then recovered and made a brilliant operative recovery. For three weeks he passed large amounts of urine daily from the loin tube but none from the bladder. From the bladder washings streptococci were obtained. A second cystoscopy revealed nothing new. Then he began to urinate as much as 700 c.c. in twelve hours. I therefore removed the tube and in a week the sinus closed, whereupon the temperature went to 105° and the loin reopened, so I replaced the tube and left it in.

"In July, five months after the first operation, he returned to the hospital, still passing all the urine through the left loin. I reopened the loin, found the kidney very adherent and the sinus entering the center of the cortex. I mobilized the lower pole subcapsularly, disclosed the adherent pelvis and the ureter moderately dilated below a narrow tight stricture at the ureteropelvic junction. I opened the ureter and found that I could not pass even a probe through the stricture. I hoped to do a plastic operation, but found that I could not mobilize the ureter or kidney sufficiently to do so. I therefore made another incision an inch down the ureter and introduced a No. 20 F. catheter through this up into the pelvis of the kidney, thus splinting the stricture wide open. This tube was left in for three days. Thereafter most of the urine came from the urethra, but four days later his temperature rose to 104° and remained thereabouts for three days, when he passed a small phosphatic stone. His loin then promptly healed and his convalescence thereafter was uneventful.

"Two years later, in July 1917, after a week of pain and fever in the left loin, he returned. I watched him for ten days, during which he had irregular fever, each relapse of temperature being accompanied by pain in the loin and definite anuria, the longest period of anuria being twenty-four hours. Roentgen rays showed three shadows in the region of the left kidney, two of them regarded as stones. I opened the loin for the third time, found the kidney so bound down that I could hardly budge it, opened it through the old nephrotomy wound and found but one stone, stuck in the orifice of the perfectly patent ureter. The convalescence was entirely uneventful except that I had to irrigate the pelvis of the kidney once through a ureter catheter to re-establish ureteral drainage.

"In 1921, five years after his first operation, he remained entirely well, at work and weighing 200 pounds, but I have had no opportunity to make any examination, except to look at his urine, which showed no pus to the eye."

Dr. Keyes again reported this case before the New York Academy of Medicine in 1940. In May, 1942, the patient reported himself as still in excellent health 25 years after the operation, having had no further treatment in the meantime. Figure 15 shows an intravenous urogram taken in 1928 in which the excellent contour of the upper ureter may be noted.

I also found that McArthur, in 1925, reported the repair of a completely ruptured urethra, with loss of substance. He bridged the gap with a ureteral catheter "of good size." In the roentgenogram in his article it appears to be a No. 6. The kidney pelvis was drained separately by another tube. The ends of the ureter were drawn as closely together as possible, but failed to meet by ¾ inch. The splint was left in place 9 weeks. The patient became and remained well, but unfortunately no postoperative urine examinations, functional tests, or roentgenograms were reported. McArthur used this method because he had tried it successfully in reconstructing the bile ducts. This case is included because the operative procedure is really based on the same underlying principle as in my own operations.

Dr. Keyes assures me that he improvised his operation in 1915, as I did in my first case, for lack of anything better which could be done. The results, in his case, and now in mine, indicate clearly that it is an extremely valuable procedure, that it has wide applications, and that it may be depended upon to produce good effects. The principle involved is quite different from that followed in plastic operations, in which tissues are divided and then reconstructed by sutures in a more suit-

able form. If the sutures fail to hold the tissues in their new positions until healing occurs, the operation is a failure.

In the intubated ureterotomy, no effort is made to draw the tissues into a new form, and no sutures are used. The operation depends upon the physiological repair processes of the tissues. The splint is a mold upon which the tissues, by their own proliferation, re-form the ureteral channel in normal size and shape. It must be left in place, therefore, until this proliferation is completed, and the new channel lined by epithelium. The data presented in this paper prove that this actually occurs, and that a new and normal size channel replaces the old, strictured one.

One wonders, however, whether the muscular layers of the ureteral wall also proliferate about the tube splint. If not, a considerable segment of the ureteral wall in the operative area would be devoid of muscular coats. Such a new formed ureter would be incapable of peristalsis, which might interfere with the transport of urine through the ureter. Unfortunately, it has not been possible to perform any experimental work on this problem, and no pathological material is as yet available from any of the patients who have been operated upon. One can only say that urinary drainage from the renal pelvis is free enough so that the urine has become clear and sterile in 4 of the reported cases, and possibly in the other, and that intravenous urograms give no evidence of any urinary stasis due to changes in the ureter (Figs. 3b, 7, 10, 14).

In the use of a ureteral or ureteropelvic splint, the size of the splint, its shape, and the length of time it is left in place are the most important points. I believe that many tubes used as splints have been too small. It seems reasonable that a tube used for this purpose should be as large as will enter the uncut, or presumably normal, part of the ureter without fitting so tightly as to cause ischemia of its wall. It may well be that specially shaped splints, including perhaps conical ones for the ureteropelvic junction, will prove to be useful. If a splint is withdrawn too soon, it will fail of its purpose. The allowance of time for the tissues to reconstruct themselves about it should be generous, erring on the side of too long rather than on the side of too short. Three weeks may be enough, but should be regarded as a minimum. I believe it will seldom be necessary to leave a splint in place more than 4 or 5 weeks.

This method is presented in the expectation that it will prove to be a very valuable means of dealing with all kinds of ureteral and ureteropelvic stenoses, including those not amenable to any other method of treatment. Indeed, in the Jefferson Hospital urological department, operations done according to this method have entirely superseded all plastic operations on the ureter and ureteropelvic junction. We find the technique much simpler, the results much more certain. The provision of fully adequate, continuous drainage for the urine during the period the splint tube remains in place is essential to success. If this is done, there are remarkably few complications and difficulties.

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THE INTRAPERITONEAL ADMINISTRATION OF SULFADIAZINE

With Special Reference to a Comparative Study with Sulfanilamide

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THE introduction of new sulfonamide compounds at short intervals makes it necessary not only to study their various characteristics—dosage, therapeutic effect, toxicity, etc., but also to make a comparative experimental and clinical study so that we may know when each should be used and how. The synthesis and introduction of sulfadiazine by Roblin and associates, and the very favorable pharmacological and therapeutic report by Feinstone and associates led us to conduct a study of the drug; we were particularly interested in its comparative usefulness when implanted into the peritoneal cavity following operations in which contamination, such as that resulting from resection of the bowel, was sustained.

The wide bacterial specificity of sulfadiazine, as reported by Long, McSwain and Glenn, and others represents a distinct advantage over other sulfonamides. Wheeler and Plummer noted that the proportion of the acetylated drug in the blood and urine was lower than with any other sulfonamide compound, except one; this may explain the relatively high degree of therapeutic effectiveness with sulfadiazine. The relatively low toxicity and high blood levels per kilogram unit of dose as reported by numerous observers (3, 10, 11) is in complete agreement with the experience of the authors. Although the relative toxicity of sulfadiazine is less than that of sulfanilamide, sulfapyridine, or sulfathiazole, yet one of the toxic complications of sulfonamide therapy, namely, renal damage (9, 13, 16, 17), occurs with a greater frequency than with sulfanilamide, and at about the same frequency as with sulfathiazole. However, the authors have not observed a single instance of renal injury in the cases reported herein. In a patient not included in this report we did note oliguria which was relieved by ureteral catheterization and fluids. The patient, a young girl who previously had had one kidney removed for an actinomycotic abscess probably should have had a smaller dose or none at all. Although renal injury as manifested by one or more of such manifestations as albuminuria, blood in the urine, oliguria, anuria, etc., occurs more frequently following sulfadiazine than after sulfanilamide, other toxic manifestations—e.g., headache, vertigo, fever, nausea, vomiting, mental confusion, weakness, etc.—are much less frequently encountered. Jaundice and concomitant hepatic damage, which have been reported with such a high incidence with intraperitoneal sulfanilamide therapy by Jackson and Coller and others, have not been encountered by us with sulfadiazine.

There are innumerable reports in the medical literature regarding the effect of the sulfonamide compounds on wound healing; although some of these reports are contradictory, most of them claim little or no detrimental effect. The recent report of Jacoby and associates describing no inhibition of the growth of epithelial cells in a tissue culture media saturated with a sulfonamide compound revealed no inhibition with sulfapyridine or sulfadiazine. The greatest inhibition of cellular growth in a sulfonamide solution was in the media containing sulfathiazole. On the other hand, addition of proflavine to the media, in concentrations used clinically, resulted in death of the cells. They found that the concentration of proflavine which would barely permit epithelial growth was between 1:100,000 and 1:120,000. The present au-

From the Department of Surgery, College of Medicine, University of Illinois. Aided by a Grant from the Graduate School of the University of Illinois. The sulfadiazine was kindly furnished by Sharp & Dohme.

thors are inclined to attach much significance to these experiments from the standpoint of wound toxicity, interpreting them as indicating a very low degree of toxicity to tissue cells in a wound.

Sulfanilamide (6, 19) is being used more frequently at the present time for intraperitoneal implantation than is any other sulfonamide, although sulfapyridine (5) and sulfathiazole (2) are also being used. If the latter drug is used, it should be implanted in the form of an emulsion (2) because of its tendency to "cake" and act as a foreign body. Regardless of which drug is used for intraperitoneal implantation it should be emphasized that the drug must be sterilized by steam pressure to prevent development of anaerobic infection. In the crystalline form, none of the sulfonamides has any deleterious effect on anaerobic organisms. The development of a fatal case of tetanus following the intraperitoneal implantation of nonsterile sulfapyridine (contaminated by the container), as reported by Atkinson, proves the necessity of sterilization.

The present authors are aware of only one report dealing with the intraperitoneal use of sulfadiazine; this is a report by Mulholland and associates (15) describing intraperitoneal use of the drug in 6 cases. They used doses ranging from 5 to 20 grams, but advised against doses as high as 20 grams. The study which we have conducted represents experimental observations which have been made on absorption time and intraperitoneal reaction in the dog, and a comparative study of 68 cases in which sulfadiazine was used intraperitoneally, and of 62 cases in which sulfanilamide was used.

EXPERIMENTAL METHODS AND RESULTS

In a series of 10 dogs a suspension of sulfadiazine in sterile water was introduced under aseptic technique into the peritoneal cavity by means of a trochar. The dose employed in these experiments was 0.15 gram per kilogram of body weight, which is slightly higher than the dose finally adopted for the human. This amount was suspended in 100 cubic centimeters of sterile water and introduced through the trochar. The absorption of the drug was studied by blood level determinations at 2 to 4 hour intervals. The animals were killed at various intervals by means of intravenous nembutal, and the peritoneal cavity was inspected. Note was made of the amount of the drug which was unabsorbed. Sections for microscopic study were taken from all abdominal viscera and the peritoneum.

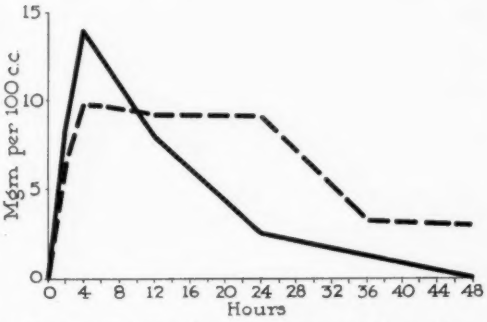

Chart 1. Note that the peak blood level of the two drugs in dogs is reached at about the same time, but is slightly higher with sulfanilamide (—). However, it falls rapidly below the sulfadiazine (———) level which is sustained longer. The dose with each drug was 0.15 gram per kilogram, given intraperitoneally.

It will be noted in these experiments that there was prompt rise to a peak of 9.8 milligrams in 4 hours (see Chart 1), followed by a slow drop to 3.0 milligrams in 48 hours. Comparison with the curve representing the average blood levels in 5 dogs that had sulfanilamide implanted into the peritoneal cavity in the same dose, reveals that the peak is reached in the same time, but the sulfadiazine level is somewhat lower. It will be noted, however, that the blood level when sulfadiazine is used persists at a higher level, and for a longer time.

Two dogs were operated on 24 hours after injection of the sulfadiazine emulsion, and the peritoneal cavity was inspected. It was estimated that 50 per cent of the drug remained unabsorbed. The omentum was adherent to the site of the trochar puncture. Small clumps of the drug were scattered throughout the mesentery of the bowel, and in several areas they were covered by the tissue of the mesentery. Encased in the omentum were many small clumps of the drug up to 3 milli-

meters in size. These clumps were easily scraped off wherever they were attached. There was no free peritoneal fluid, and there were no adhesions.

Two different dogs observed 48 hours after injection of the emulsion revealed that small masses of the drug were still encased by the omentum especially at the site of the trochar puncture. A few specks were adherent to the serosa of the bowel. No free peritoneal fluid was present. Between 30 and 40 per cent of the drug was present. In 4 days there were 6 to 10 flecks of the drug still present in 3 dogs observed. They were firmly attached in some areas, and seemed to be surrounded by the tissue of the omentum or the mesentery. A few flecks were adherent to the serosa of the small bowel. There was no gross sign of change in the serosa surrounding the site of these attachments. No free peritoneal fluid was present. The 3 remaining dogs were sacrificed in 7 days. Two small masses of the drug were encased in omentum in 1 dog and 3 similar clumps in each of the 2 others. These clumps were about a half centimeter in size. There were no adhesions except that the omentum was adherent at the site of the trochar puncture.

Microscopic sections of tissue (chiefly omentum) surrounding the sulfadiazine crystals were essentially negative in all instances except that on the 7th day a typical foreign body reaction was present with lymphocytic infiltration and foreign body giant cells.

Five dogs had sulfanilamide implanted into the peritoneal cavity by a similar technique to compare this drug with sulfadiazine. Autopsy 24 hours after implantation of the drug revealed no evidence whatsoever of the drug; all of it had been dissolved and apparently absorbed. There were no adhesions; the serosa of the bowel and all of the abdominal viscera were normal. There was no free fluid. Observations in animals 2 days, 4 days, 7 days, and 3 weeks after implantation of the drug revealed identical findings.

In addition to the experiments described, 20 dogs were operated upon and 4.5 grams of sulfadiazine placed in the peritoneal cavity directly. These experiments were done to simulate as closely as possible the method used in the human, both in the amount of the drug used, and in the method of placing the drug into the peritoneal cavity. Although the actual dose adopted for use in the human was 6 grams, the animal dose per kilogram of body weight is roughly three times the human dose, and the dose per square foot of peritoneal surface, at least 5 times the human. All sulfadiazine used in these experiments had been sterilized by autoclaving for 15 minutes at 15 pounds pressure with a temperature of 119 degrees centigrade. It had previously been determined by one of us (L. W.) through animal experiments, that sulfonamides which were so heated suffered no loss of their therapeutic effectiveness.

Two dogs were sacrificed in 24 hours. It was estimated that 3 grams of the drug remained in the peritoneal cavity of each dog. The drug was again in the form of clumps adherent loosely to serosal surfaces of the bowel, liver, mesentery, and peritoneum. Omentum had already surrounded the material in several areas. No free peritoneal fluid was present. Examination of 2 dogs in 48 hours revealed an estimated 2 grams of drug remaining. At the operative site of one dog there was a tangled mass of bowel adherent to the omentum and to adjacent loops. These adhesions were easily separated and there was no apparent gross pathological change on the serosa at the points of contact. Clumps of the drug were surrounded by the omentum in several other areas. At 72 hours, examination of 2 dogs revealed about 1 gram of drug still present in each. At the point of omental attachment to the operative site in 1, there was a mass of drug measuring 2 by 3 centimeters encased in the omentum. Smaller masses up to 2 millimeters in size were adherent to the serosa of the bowel and the liver in both dogs, and the bowel in several places was loosely adherent where the drug was interposed between 2 serosal surfaces. Operation upon 2 dogs 5 days after implantation of sulfadiazine revealed omentum to be adherent to the operative site; at this point, the small bowel was attached to the omentum by soft adhesions. When these adhesions were separated, small masses of the drug were revealed to be interposed between the omentum and bowel and

between the loops of the bowel. On the right parietal peritoneum in 1 dog an adhesion was present between the small bowel and the parietal peritoneum. Small clumps of the drug were interposed at this adhesion also. Autopsy performed on these animals 9 weeks later revealed the omentum still attached to the operative site, but all adhesions and all of the drug clumps had completely disappeared. The adhesion to the suture line is considered incidental to the operation and not related to drug action. All viscera were normal in appearance. Autopsy on 2 dogs at 8 days revealed a loose adhesion of small bowel in each dog attached to the parietal peritoneum on the left side. Sulfadiazine clumps were present at the site of the adhesions, and several small clumps were incorporated in the omentum. In 2 dogs operated upon 10 days after implantation of sulfadiazine no crystals could be found in either case. There were no adhesions, and the loops of bowel appeared normal. Autopsy on these animals 3 months later revealed normal peritoneal cavity. Eight animals were sacrificed after 3 months. The findings in each of these animals were identical: there were no clumps of drug remaining, there were no adhesions present, and all viscera appeared to be normal.

Microscopic examinations of the tissues were negative except again a foreign body reaction was noted around the sites where the drug was surrounded by omentum or peritoneum.

Blood level determinations on 5 dogs, given 0.5 gram sulfadiazine per kilogram, are represented in Chart 2. It will be noted that with this high dose the blood level rises slowly until it reaches a peak of 40 milligrams per cent in 4 days, and then slowly falls until after a period of 8 days the blood level has reached 2 milligrams.

There were no toxic effects noted in any of the dogs following the administration of the smaller dose. With the large dose (5 times the dose adopted for clinical use) only 2 of the 20 dogs gave evidence of toxicity; this consisted of anorexia and some vomiting in the first 24 hours. All dogs made completely satisfactory recoveries from operation and reacted normally subsequently.

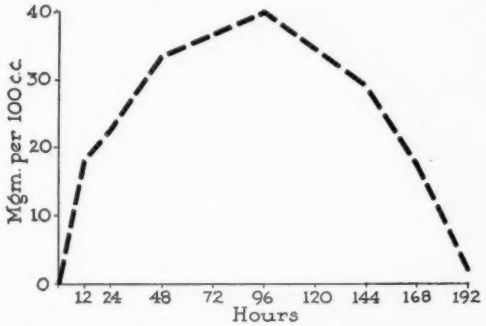

Chart 2. With such a large dose (in dogs)—0.5 gram sulfadiazine per kilogram into peritoneal cavity—the peak blood level does not occur until after 96 hours as compared to 4 hours after a dose of 0.15 gram per kilogram (see Chart 1).

CLINICAL METHODS AND RESULTS

Attempt was made to compare the relative efficiency of sulfadiazine with sulfanilamide when used in the peritoneal cavity of human beings following laparotomies. In general, the drugs were used only in operations in which contamination had taken place. During the period of experimentation a few clean cases were used, but the authors realize that sulfanilamide therapy in these cases as a routine is superfluous, and in routine work should not be used. Altogether sulfadiazine was used in 68 cases, and sulfanilamide in 62 (Table I). Of

TABLE I.—COMPARATIVE EFFICIENCY OF INTRAPERITONEAL USE OF SULFADIAZINE AND SULFANILAMIDE

	Sulfadiazine	Sulfanilamide
Number of cases	68	62
Contaminated	52	39
Clean	16	23
Infected wounds	3*	9†
Severe	0	6
Mild	3	3
Wound disruption	1	0
Peritonitis	1	0

*4.4 per cent; †14.5 per cent.

the 68 cases in which sulfadiazine was used 52 represented contaminated cases, and 16 clean cases. Of the 62 cases in which sulfanilamide was used 39 were contaminated, and 23 clean. In the contaminated group we included such cases as resection of the stomach, resection of the colon, gastrostomies, gastroenterostomies, resection of the ileum, etc. Cholecystectomies,

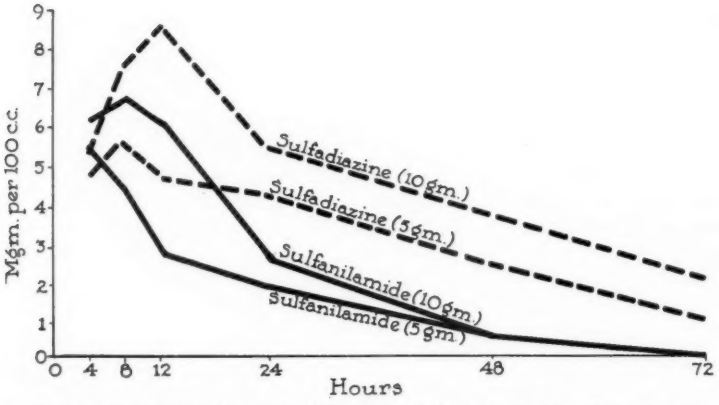

Chart 3. Note that in the human being the peak blood level with sulfadiazine is as high, in fact higher than with sulfanilamide; the blood level is prolonged longer with sulfadiazine.

herniotomies and appendectomies for nonperforated appendicitis made up most of the so called clean cases. Attempt was made to get about the same ratio of various types of operations in the 2 series. It will be noted, however, that there were many more contaminated cases in the sulfadiazine series indicating that the sulfanilamide series should have an obvious advantage over the sulfadiazine series.

Table I reveals that there were 3 infections in the sulfadiazine series, all of which were relatively mild. In the sulfanilamide series there were 9 infections, only 3 of which could be considered mild. In the sulfadiazine series there was an incidence of infection in 4.4 per cent of the cases, and an incidence of 14.5 per cent in the sulfanilamide series. Sulfadiazine was obviously much more effective in the prophylaxis of infection. However, in the sulfadiazine series there was 1 case of wound disruption and 1 case of peritonitis which resulted fatally. The patient whose wound disrupted was an inoperable carcinoma of the stomach upon whom a gastroenterostomy had been performed. From experience we know that most instances of wound disruption occur in such patients. Since there is only 1 case of wound disruption, we doubt therefore that its incidence was anything more than a coincidental occurrence. The patient who developed a peritonitis following sulfadiazine implantation in the peritoneal cavity had an operation for an intestinal fistula. A small abscess and numerous areas of acute inflammation were found in the left lower quadrant. We feel that this fatality in reality resulted from an error in the time of operation and the amount of operative work; attempt was made to separate adhesions relieving a probable partial obstruction. In retrospect, the process should have been allowed to resolve more before manipulation of this degree was undertaken.

There are many reports in the literature regarding the irritating effect of sulfonamide compounds on tissues, particularly regarding the drainage of serosanguineous material from wounds in which they have been implanted. We encountered one instance of excess exudation of fluid from the wound with sulfadiazine, and 3 with sulfanilamide. In all instances, however, the drainage stopped after 3 or 4 days and the wound healed *per primam*. We consider that this drainage is usually an expression of the use of too much sulfonamide compound. In the case of the insoluble compounds such as sulfadiazine and sulfathiazole extensive drainage is probably caused by failure to distribute the drug evenly about the wound. If it is put in the wound in such large quantities in local areas that clumping can occur, the residual lump will act as a foreign body or result in a dead space after the drug is

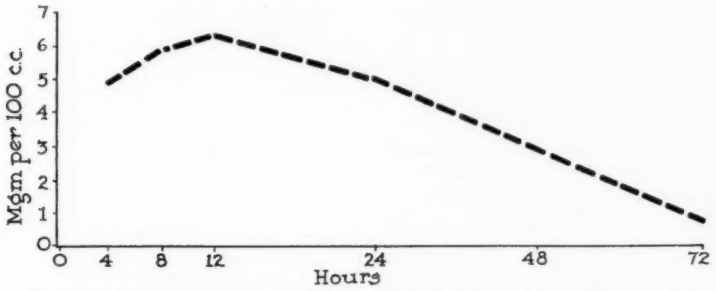

Chart 4. Average blood level (free) in the dose of sulfadiazine, 6 grams, adopted for routine use. Of the 6 grams used (in the human being) about 4 grams are placed in the peritoneal cavity and 2 in the wound.

absorbed. We are firmly convinced, therefore, that the sulfonamides must be distributed very evenly over the surface of the wound or in the peritoneal cavity.

The dose used varied between 5 and 10 grams. After analyses of the results with the larger doses we could not see any evidence of a greater efficiency with such doses and, for sulfadiazine, finally decided upon a dose of 6 grams. We usually place about 4 grams inside the peritoneal cavity and utilize 2 grams for insertion in the wound. It is now fully realized that peritonitis will not develop even after a contaminating operation such as resection of the stomach, etc., unless there has been contamination of an unusual degree occurring only through carelessness. This carelessness might extend into leakage of the suture line through technical defects. On the other hand, we have seen infections of the wound develop when contamination appeared minimal. This is simply an expression of the well known fact that the peritoneal cavity tolerates contamination much better than do the tissues of the abdominal wall.

Blood level determinations were made to determine the amount of sulfonamide in the blood, and the duration of the respective levels. Chart 3 illustrates a comparison of the blood levels after the use of sulfadiazine and sulfanilamide. It will be noted that the peak level following 10 grams of sulfadiazine was 8.6 milligrams per 100 cubic centimeters, whereas the peak level following 10 grams of sulfanilamide rose only to 6.8. In the case of sulfadiazine the peak was established at 12 hours whereas with sulfanilamide the peak was established in 8 hours. This difference in the peak level is, no doubt, related to the difference in solubility. In the case of the 5 gram dose the peak level of the two drugs was practically the same but delayed slightly with sulfadiazine. In either dose it will be noted that a much higher level persisted with sulfadiazine than with sulfanilamide. As a matter of fact, after the first few hours the blood level following 5 grams of sulfadiazine was higher than following 10 grams of sulfanilamide and persisted longer. Since the effect of local implantation of sulfonamide compounds is bacteriostatic and only very slightly bactericidal (if at all), the high blood concentration *for a few hours* which is so characteristic of sulfanilamide *would not appear to be of any advantage.* On the contrary it would appear that a *persistent blood level* in the effective range *would be much more desirable*, since the chief effect of a sulfonamide is bacteriostatic and therefore *must extend over a long period of time to be most effective.* Under these circumstances a dose of 5 grams of sulfadiazine would appear to be fully as effective as a dose of 10 grams of sulfanilamide.

After reconsideration of the various doses we finally decided upon a dose of 6 grams of sulfadiazine for intraperitoneal use, 1 or 2 of the 6 grams being used for implantation in the wound. The peak level for this dose, as noted in Chart 4, was 6.2 milligrams per 100 cubic centimeters, and occurred at 12 hours. The amount gradually diminished to 3.2 at 48 hours and dropped to slightly more than 1

milligram per 100 cubic centimeters at 72 hours.

ANALYSIS OF RESULTS

As noted in Charts 1 and 2, the type of curve following local implantation of a sulfonamide compound varies markedly with the dose. As the dose is increased, the peak level is delayed. There are likewise additional factors controlling the type of curve. The amount of surface area over which the drug is implanted is probably one of the most important of these remaining factors. However, even though these factors be controlled, there is still a wide variation in the peak level and persistence of blood levels with all sulfonamide compounds; this fact has been observed by numerous investigators. In Chart 1 it will be noted that following the implantation of 0.15 gram of sulfadiazine per kilogram of body weight in a dog, the blood level rose to 9.8 milligrams per 100 cubic centimeters and persisted for 48 hours, at which time it had dropped to 3.8. This level is not significantly different from the level in a human being with an equivalent dose. There is one difference, however, in so far as the peak level in the dog is reached in 4 hours instead of 12 hours in the human being. This increase in the absorption is related to animal species.

Sulfadiazine persists in the peritoneal cavity of the dog for several days. At points where the drug has collected or was not spread out evenly over the peritoneal surface the omentum becomes adherent as it would around any foreign body. However, observation of these animals after absorption of the drug always revealed complete obliteration of these adhesions. They were never dense in the first place, and in the authors' opinion would not result in intestinal obstruction.[1] No free fluid beyond normal quantities was ever noted in the abdominal cavity of the animals. At no time did we find evidence of lack of healing either in animals or in human beings.

As stated previously, the incidence of infection in our clinical experience was greater following the use of sulfanilamide than following sulfadiazine. We believe the difference in this incidence is sufficiently great to be more than coincidental, and are convinced that, at least in our experience, sulfadiazine was superior to sulfanilamide. When sulfadiazine is used it should be spread evenly over the surface so that it will not accumulate in large clumps. A foreign body reaction in the omentum surrounding clumps of sulfadiazine was noted in our experiments. Sulfonamides including sulfadiazine have been used experimentally on brain tissue by Russell and Falconer, Taffel and German, and others, and the same foreign body reaction observed, but without any significant inflammatory reaction.

A recent preliminary report by Fox suggests that sodium sulfadiazine might be used in place of sulfadiazine for implantation in wounds. The authors realize that faster absorption would be obtained, but doubt whether the difference in a few hours would be significant since the drug is primarily bacteriostatic and not bactericidal. It appears obvious that if the drug used for implantation in tissues is extremely soluble, the tissues will be exposed to a very hypertonic solution and thereby might be damaged.

Opinions would no doubt differ as to the optimum characteristics desired in a drug for intraperitoneal use. However, all would agree that such a drug must be relatively free from toxicity in effective doses. Sulfanilamide and sulfadiazine each would qualify in this respect. We are of the opinion that a drug which has a blood level of prolonged duration is superior to one with a shorter one. Since the primary mode of action of the sulfonamides is because of their bacteriostatic action and not bactericidal effect, we can see no advantage in a relatively high blood level (perhaps above the effective therapeutic range) if it recedes rapidly (in a few hours) to a level below the effective range. If this reasoning is sound, sulfadiazine has an advantage over sulfanilamide, since the blood level following the latter is much less persistent. Naturally, the dose of sulfanilamide might be repeated, but it cannot be implanted into the peritoneal cavity or wound except at the time of operation. Any of the drugs may be given parenterally (sulfanilamide by vein and subcutaneously, and

[1]Since analyzing the data herein given, about 150 additional cases of intraperitoneal implantation of sulfadiazine have been observed. We have not observed a single instance of postoperative intestinal obstruction in either series.

sodium sulfadiazine by vein), after the operation, but *this therapy would have to be resumed earlier in the case of sulfanilamide than in the case of sulfadiazine.*

Sulfadiazine has another advantage over sulfanilamide in so far as a given blood level is reached and maintained with a smaller dose than with sulfanilamide. Toxic symptoms such as headache, nausea, vomiting, fever, cyanosis, etc., are more common with sulfanilamide but renal complications are more common following sulfadiazine therapy. However, in the series herein reported we did not observe a single instance of renal complication. We are convinced that *if high doses of sulfadiazine are to be given, a fully adequate fluid intake (3000 c.c. per day for an adult) must be maintained.*

Sulfadiazine has a much wider range of specificity than sulfanilamide, being effective against the hemolytic streptococcus (3, 10, 11) as well as many other bacteria. Although the peak level may be reached a few hours earlier with sulfanilamide than with sulfadiazine, this would not appear to be an advantage *from a prophylactic standpoint,* although it would, no doubt, be of advantage if an infection were already present.

About the only disadvantage possessed by sulfadiazine would appear to be its persistence in the wound for several days—a feature caused by its relative insolubility. However, we are by no means convinced that this feature is a disadvantage, as long as the drug is distributed evenly throughout the peritoneal cavity and wound, and not dumped in one place, thus creating a foreign body effect. It appears likely that "lumping" of the drug would likewise be disadvantageous in the case of sulfanilamide, but through another mechanism; namely, exposure of tissue to a concentrated solution of the drug, resulting from its greater solubility.

SUMMARY

Sulfadiazine crystals were implanted in the peritoneal cavity and wounds of 68 patients operated on for various lesions, most of which resulted in peritoneal contamination. A similar study in which 62 patients were used was conducted with sulfanilamide. In the series studied we obtained an incidence of wound infection of 4.04 per cent with sulfadiazine and 14.05 per cent with sulfanilamide. Since there were more contaminated cases in the sulfadiazine series it appears definite that at least in our experience, sulfadiazine was superior to sulfanilamide in the prevention of wound infection. However, in the sulfadiazine series there was 1 wound disruption, and 1 case of fatal peritonitis. We believe, however, that these 2 cases are coincidental, and doubt that they are related to the use of sulfadiazine. No toxicity of any kind was noted with the sulfadiazine, neither was there any evidence of delay in wound healing. After study of blood levels, etc., we finally adopted 6 grams as the routine dose; we implanted 4 grams in the peritoneal cavity, and 2 grams in the wound at the end of the operation. It should be emphasized that all sulfonamides should be sprinkled evenly over the surface of wounds. Particularly is this true of the less soluble compounds such as sulfadiazine.

Our studies on animals, as well as on human beings, revealed a much more persistent blood level with sulfadiazine than with sulfanilamide. In our observations on the human, we noted that the blood level following 5 grams of sulfadiazine intraperitoneally was higher than the blood level following sulfanilamide.

In our experience, sulfadiazine is less toxic than sulfanilamide. We believe that the greater persistence of the blood level of sulfadiazine over sulfanilamide makes the former drug superior to the latter for implantation in the peritoneal cavity and wound following laparotomy, particularly when we consider that the beneficial effect of the sulfonamide compounds is primarily bacteriostatic and only slightly bactericidal.

In our experience the use of sulfonamides in wounds contaminated by resection of bowel has resulted in a much lower incidence of infection, sulfadiazine being superior to sulfanilamide.

If sulfonamide action is desired for a few days following operation and intraperitoneal use of the drug therapy must be resumed more rapidly with sulfanilamide (usually subcutaneously or intravenously in 0.5 to 0.9 per cent solution in physiologic saline solution)

than with sulfadiazine. The common method of administering sulfadiazine under such circumstances is to give sodium sulfadiazine intravenously (e.g. 3 grams twice daily).

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A STATISTICAL METHOD FOR EVALUATING THE RESULTS OF TREATMENT FOR PEPTIC ULCER

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DURING the past two decades the various methods of treating peptic ulcer, both medical and surgical, have been marked by persistent and widespread disagreement regarding their merits. As yet a certain cure for this disease remains unknown, for none of these therapeutic measures can assure the patient against a recurrence of his disorder. It happens not infrequently that a patient remains free of symptoms for 20 or 30 years, only to experience a recurrence of ulceration after such a long interval. Hence, the effect of such therapeutic procedures cannot be evaluated on the basis of definite and permanent cures but only on the chances of the patient's remaining free from recurrence for a limited time interval. Furthermore, the measure of therapeutic efficacy is influenced by a multiplicity of causes, and for this reason any attempt to evaluate it quantitatively resolves itself of necessity into a statistical (i.e., biometrical) problem.

Now, statistics in a technical sense is not merely the compilation of data from hospital records and the computation of "percentages" —by some haphazard procedure. Rather, it implies the utilization of a logical, well conceived technique for the numerical representation and evaluation of such case records, according to certain well established mathematical principles known as *statistical methods*.

The essence of this technique is very well expressed by the following quotation from A. Bradford Hill's *Principles of Medical Statistics*: "Whereas the laboratory worker can frequently exclude variables in which he is not interested and confine his attention to one or more controlled factors at a time, the clinician and social worker have to use records which they know may be influenced by factors which they cannot control but have essentially to be taken into account. The essence of the statistical method lies in the elucidation of the effects of these multiple causes. . . . The statistical method is required in the interpretation of figures which are at the mercy of numerous influences, and its object is to determine whether individual influences can be isolated and their effects measured. The essence of the method lies in the determination that we are really comparing like with like, and that we have not overlooked a relevant factor which is present in Group A and absent from Group B."

In short, statistics are "quantitative data affected to a marked extent by a multiplicity of causes" and statistical methods are "methods especially adapted to the elucidation of such data." (Yule and Kendall).

Failure to recognize this fact is in no way restricted to the ulcer problem, but it exists in virtually every similar field of clinical investigation. We feel that the present confusion in evaluating different therapeutic procedures for peptic ulcer must be ascribed in a great measure to the disregard of this basic idea regarding methodology. Hence, any further efforts in this direction must be approached in the light of a statistical technique which fulfills the requirements of accepted "statistical theory." Unless this premise be generally accepted, there is no reason to expect that future efforts will be any more productive of conclusive results than those of the past have been.

In order to grasp the implications of this point of view more fully, let us review the procedures which have hitherto been employed for evaluating surgical methods for ulcer therapy. It is only by trial and error that clinicians have come to recognize the manifold, and sometimes intangible, nature of the factors which influence the quantitative appraisal of the results of treatment. As fallacies in the methods for evaluating results have come to light, efforts have been made to correct them, but the evolutionary nature of this process has not been generally recognized because each investigator focused attention

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only on a particular weakness which he perceived in the methods of his predecessors. Thus, it was early recognized that, in the case of a disease like peptic ulcer in which there is no certainty of cure, the post-therapeutic time exercises a most important influence on the numerical evaluation of success or failure. Likewise, the need for careful personal and continuous follow-up observation for the detection and reliable interpretation of recurrent complaints was not appreciated until experience had revealed that peptic ulcer is a disease of remissions and recrudescenses, and that its manifestations may be simulated by other disorders. In the course of time it became apparent that the character of the clinical material selected for treatment and for study exerts most important influence on the measures of the risk and of the end-results of treatment. Throughout the years, various observers have employed different criteria for evaluating the effectiveness of peptic ulcer therapy. As a consequence, there has been no standardization of criteria so as to permit of valid comparison of results reported by different clinics. And finally, little consideration has been given to the element of chance or probability which enters into the results obtained with any single group of patients, considered as a sample of the universal population of all such patients; i.e., the concept of random sampling has been generally neglected.

Specifically, the following are the more striking weaknesses in the methods which have been employed in studying the end-results of treatment:

1. Many of the earlier reports disregarded the ever present possibility of a recurrence and the importance of postoperative time in following cases. This is well illustrated by the frequent report of results in such terms as "cases followed for one to ten years—80 per cent cured."

2. When the importance of the time factor first came to be recognized, therapeutic success was sometimes evaluated on the basis of the results after a poorly defined time interval. Thus, one writer classified his follow-up data on the basis of "early and late results—less than or more than one year postoperative," another employed "no less than a 5 year follow-up," and a third group of investigators used the time interval of their own actual experience as a basis for measuring their surgical results. In all these reports, however, the time was represented by an average or a limiting value for the entire group and not by a time interval which held for all the patients individually; e.g., "cases for an average of 7.1 years—none less than 2 years and some for as long as 12 years." In other words, the sample population of the entire study was made up of individuals who had survived the operation for different lengths of time and therefore were not truly comparable in this respect. In another instance, in one of the best studies of the results of surgery for peptic ulcer that we know of, average follow-up periods of 5.4, 6.3, 3.3, etc. years are given, whereas the observations on which these averages were based varied from 1 to 15 years.

3. In an effort to circumvent the fallacy of conclusions based upon a follow-up of inadequate duration, some writers adopted an arbitrary period of observation for every case in the group as the necessary *lower limit* for establishing the permanence of a therapeutic result; e.g. "cases followed for a minimum of five years." The validity of such a limited interval as an overall measure of success has always been assumed without any formal justification.

4. The latest and most constructive improvement in statistical technique for evaluating ulcer therapy is contained in the principle termed "follow-up in continuity" by St. John and his associates (3, 4). According to this principle every patient must be seen at repeated and fairly regular intervals, so that the course of his postoperative history can be followed with the progress of time. One very important consequence of this procedure might be the charting of a trend curve which shows the rate of development of failures at various times after operation. The authors failed to utilize this possibility, however, and merely calculated their results in terms of an average follow-up time.

The foregoing review of the various ways in which observers have estimated the results of therapy for peptic ulcer indicates clearly the weaknesses and fallacies of such statistical data. In view of this situation we set ourselves

the problem of devising a statistical procedure which will avoid most of the weaknesses in the methods previously employed for this purpose. The result of our labors has been a method for measuring the success of any therapeutic procedure for a nonmalignant disease which may recur at any time during the life of the patient. In the course of this work we formulated a series of fundamental conditions which must be adhered to in order to insure statistical validity, and we shall discuss these requirements before presenting the method in detail.

FUNDAMENTAL PRINCIPLES UNDERLYING THE METHOD

1. Every patient should be seen at follow-up personally and periodically (3 to 6 months), and his condition should be appraised at least once a year. In this way we obtain the number of *new failures* which have developed in the course of each year, and the corresponding total number of patients observed. From these data it is possible to construct a cumulative curve which reflects the timetrend of the recurrences, i.e., a curve for the total number (or %) of recurrences for 1, 2, 3, etc. years after operation.

2. All patients operated upon during any one calendar year (e.g., January through December, 1924) are said to fall within the same "surgical year." All observations made during the same postoperative year, *irrespective of the surgical year*, are said to fall within the same "postoperative" or "follow-up year." For example, the result in patients operated upon in 1924 and in 1930, and appraised in 1926 and in 1932 respectively, are all classified as falling in the second follow-up year. Thus, we may combine data for different surgical years provided only that the groupings are made according to follow-up rather than chronological year. Furthermore, suppose it is desired to study the therapeutic effects of an operation over a period of 15 years (or 10 years, or 5, as the case may be)—that is, the entire duration of the trend curve is set at 15 years. Then every case included in the sample population for this study must have been followed for at least this length of time. Thus, if results are available on operations performed from 1923 through 1941, and it is desired to study the postoperative course of the disease for 15 years, then the population sample chosen for this study must exclude cases of all patients operated upon after 1926—for these latter cases obviously would not yet have reached a 15 year follow-up by 1941. All patients operated upon in 1927 or thereafter afford the possibility of an independent study of shorter duration. Thus, the patients operated from 1927 through 1931 constitute a sample population which is valid for a 10 year study (but no longer). Such a 10 year trend curve may be compared with the corresponding portion of the 15 year curve in order to obtain some notion of the variation from sample to sample (i.e., the sampling error). Of course, if only a 10 year curve were desired in the first place, it might have been obtained from the combined data for 1923–1931, by discarding all data beyond the tenth follow-up year. In a similar manner the data for patients operated upon in 1932–1936 afford an opportunity for a 5 year study, which may be compared with the two previous samples, but only for this duration. By this method we have eliminated the fallacy of the "average period of follow-up." At the same time, the entire mass of data from 1923 to date has been broken down into 3 independent sample populations which, by their comparison, afford an excellent opportunity for a study of the internal consistency of the statistical procedure.

3. In actuality, such a year-by-year follow-up is impossible for every patient included in a group of surgical survivors, because a considerable proportion of them become lost to observation at varying times after the operation. The reasons for this failure to return for examination are manifold: (1) the patient may migrate to another community; (2) being free of symptoms, he may become indifferent to the requests for a follow-up; (3) sometimes, if his condition remains unimproved after a few visits to the follow-up clinic, he will seek relief elsewhere; (4) the patient may die without our knowledge. Concerning the therapeutic fate of patients in these four categories, we can make no certain statement. *We believe that the incidence of failure among this group of patients*

is no greater than among those who return to follow-up year after year (the observed group), and it may be even less. Substantiation of this *premise* is impossible; nevertheless, we believe that it is valid with a high degree of probability. Our reason for this belief is as follows: Patients sometimes return with recurrent symptoms after many years of absence from follow-up. When asked the reason for their failure to return during the interim, they have consistently stated that, being well, they saw no point in coming back. It is sometimes contended by other writers that patients are lost to follow-up chiefly because they seek treatment elsewhere for the relief of recurrent symptoms. In our experience, however, such a patient will return at least once to report his recurrent symptoms to us before going to another institution, and therefore this contention is not a valid criticism of our premise.

This problem of the "unfollowed case" is as difficult in medicostatistical studies as it is universal. It is impossible to determine the "true" percentage incidence for the entire sample when the history of a large proportion of that sample is unknown. It is possible, however, to determine the upper and lower limits of a range within which this "true" percentage must fall. Thus, if the number of failures observed in any one postoperative year be divided by the total number of patients who survived the operation initially, the ratio is the minimum possible percentage incidence of failure in this sample. It is evident that the true percentage cannot be less than this and is almost certainly greater, by reason of the unrecorded failures. On the other hand, if we divide the number of failures observed in this postoperative year by the number of patients who actually returned to follow-up, we obtain a *maximum* estimate of the true incidence. This percentage incidence is precise for the observed group alone and therefore—by the premise formulated in the previous paragraph—the true incidence for the entire group of cases is no greater than this value and it may even be less than it. These maximum and minimum measures of percentage incidence afford a pair of trend curves between which the "true" trend curve must, in all probability, fall. For practical purposes we calculate the median average for each such pair of values, and we regard the resulting median trend curve as a better estimate of the true one than either of the others.

4. Any study concerned with "failure" of a therapeutic procedure for peptic ulcer necessitates a careful definition of the criteria of failure employed. What may be considered as adequate criteria, however, is a moot question which will be discussed in detail in another publication, since its solution does not materially influence the principles underlying our present statistical procedure. Suffice it to state that for the present purpose—which is merely to illustrate a statistical technique—we have defined a failure as the case of any patient who reveals *tangible* evidence of recurrent ulceration, or who manifests symptoms which may reasonably be ascribed to such.

It frequently happens that a patient with a recorded recurrence fails after a time to return for further follow-up observation. Such patients are treated as though they had returned each year, on the principle that "once a failure, always a failure." As such, they are included in the number of patients seen in every postoperative year for the entire duration of the study.

STATISTICAL PROCEDURE

In order to describe and illustrate our method for analyzing the results of therapy for peptic ulcer, we have employed the data from the Mount Sinai Hospital for patients with duodenal ulcer who were subjected to subtotal gastrectomy during the years 1923–1934. This material covers an interval of 12 surgical years and affords a maximum follow-up time of 17 years. Since this report is concerned only with statistical methodology, a detailed description of the factors characterizing the clinical material is not requisite. Such a description will be presented later in a clinical report dealing specifically with the factors influencing the results of the operation at this hospital.

Our first concern was the determination of the recurrence-trend curve for at least 15 years after operation. For this purpose we tabu-

TABLE I.—ANNUAL INCIDENCE OF RECURRENCE OF ULCERATION FOLLOWING SUBTOTAL GASTRECTOMY FOR PRIMARY AND SECONDARY DUODENAL ULCER, SAMPLE A, SURGICAL YEARS: 1923–1925

Year of operation	1923	1924	1925	Totals
No. of survivors	18	41	38	97
Postoperative year	Summary of annual follow-up by postoperative years No. recurrences—No. cases followed			
1	0—10	0—36	0—32	0—78
2	0—10	1—34	0—25	1—69
3	2—10	1—32	0—22	3—64
4	0—10	0—27	0—21	0—58
5	1—10	0—25	0—21	1—56
6	0—9	1—23	0—21	1—53
7	0—8	0—22	0—19	0—49
8	0—8	0—20	0—19	0—47
9	0—8	0—19	0—18	0—45
10	0—8	0—19	1—17	1—44
11	0—8	0—19	0—17	0—44
12	0—8	0—19	0—16	0—43
13	0—8	0—17	0—16	0—41
14	0—8	0—17	0—14	0—39
15	0—8	0—17	0—11	0—36
16	0—8	0—15	0—11	0—34

lated the results for the surgical years 1923–1925 inclusive (sample A), disregarding all observations made after the 16th follow-up year (Table I).

The first line of the chart contains the surgical year—when the operation was performed. The second line contains the number of patients who survived operation in each surgical year; the sum of these represents the total number of survivors included in the entire sample population. The third line contains the number of new recurrences detected during the first follow-up year for each of the 3 surgical year groups, irrespective of the calendar year of observation. The corresponding number of patients who actually returned to follow-up is likewise presented in this line, after the dash. The totals for each of these two items respectively (in the last column) gives the total number of failures (0) and the total number of cases observed (78) in the first follow-up year for the entire sample A. The fourth and subsequent lines contain the same arrangement of data for each of the remaining follow-up years.

TABLE II.—ANNUAL AND CUMULATIVE PERCENTAGE INCIDENCE OF RECURRENCE AFTER SUBTOTAL GASTRECTOMY FOR PRIMARY AND SECONDARY DUODENAL ULCER, SAMPLE A, SURGICAL YEARS: 1923–1925

Follow up year	No. survivors	Cases followed		Annual incidence of new recurrences			Cumulative incidence of recurrences		
		No.	%	No.	Min. %	Max. %	Min. %	Max. %	Med. %
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
1	97	78	80.4	0	0	0	0	0	0
2	97	69	71.1	1	1.0	1.4	1.0	1.4	1.2
3	97	64	66.0	3	3.1	4.7	4.1	6.1	5.1
4	97	58	59.8	0	0	0	4.1	6.1	5.1
5	97	56	57.7	1	1.0	1.8	5.1	7.9	6.5
6	97	53	54.6	1	1.0	1.9	6.1	9.8	8.0
7	97	49	50.5	0	0	0	6.1	9.8	8.0
8	97	47	48.5	0	0	0	6.1	9.8	8.0
9	97	45	46.4	0	0	0	6.1	9.8	8.0
10	97	44	45.4	1	1.0	2.3	7.1	12.1	9.6
11	97	44	45.4	0	0	0	7.1	12.1	9.6
12	97	43	44.3	0	0	0	7.1	12.1	9.6
13	97	41	42.3	0	0	0	7.1	12.1	9.6
14	97	39	40.2	0	0	0	7.1	12.1	9.6
15	97	36	37.1	0	0	0	7.1	12.1	9.6
16	97	34	35.1	0	0	0	7.1	12.1	9.6

Column (6)=column (5) divided by column (2); column (7)=column (5) divided by column (3); column (10)=one-half the sum of columns (8) and (9).

The totals from Table I were next transferred to Table II, for the calculation of the various percentage values. Column 2 contains the total number of survivors of the operation included in this sample. The number of patients observed each postoperative year[1] is given in column 3, and the corresponding percentage, relative to the total number of survivors (i.e., the follow-up percentage), in column 4. The next column contains the actual number of recurrences detected in each follow-up year. When this number is divided by the number of survivors (from column 2) it gives the *minimum percentage recurrence* (column 6),

[1]As already stated, this number includes all previous recurrences, regardless of whether they actually returned to the follow-up clinic after recurrence had been detected.

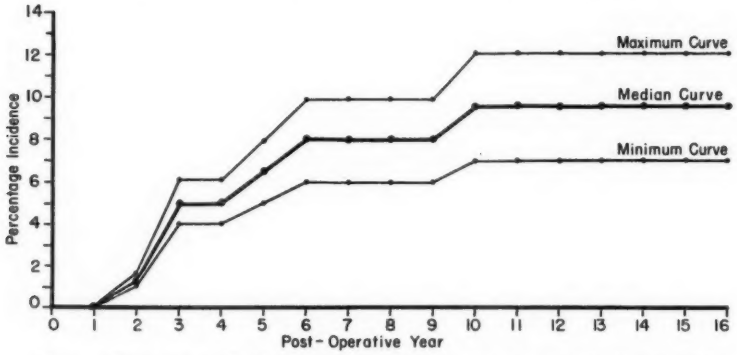

Fig. 1. Trend curves for the cumulative incidence of recurrence of ulceration following subtotal gastrectomy for duodenal ulcer. Sample A covering surgical years 1923–1925. Number of operative survivors 97.

and when it is divided by the number of patients actually seen (from column 3) we obtain the *maximum percentage recurrence* (column 7).

The next step is to accumulate the data so that they reflect the total extent of recurrence, from the first through each indicated follow-up year in turn. This must be done in terms of the percentage values and not the frequencies (the actual numbers of cases) themselves, because the former constitute an adjusted value of the latter—adjusted for the variation in number of cases followed each year. Thus, for example, the minimum percentage of recurrence (column 8) for the 7th follow-up year is obtained by adding together the percentage values from column 6 for each of the first 7 such years. The

TABLE III.—ANNUAL INCIDENCE OF RECURRENCE OF ULCERATION FOLLOWING SUBTOTAL GASTRECTOMY FOR PRIMARY AND SECONDARY DUODENAL ULCER, SAMPLE B, SURGICAL YEARS: 1926–1930

Year of operation	1926	1927	1928	1929	1930	Totals
No. of survivors	51	37	36	29	27	180
Post-operative year	Summary of annual follow-up by postoperative years No. recurrences—No. cases followed					
1	1—42	0—34	2—42	1—29	0—26	4—173
2	1—34	1—27	0—30	0—26	1—24	3—141
3	0—29	1—25	0—30	0—26	0—23	1—133
4	0—28	0—24	0—28	0—23	0—22	0—125
5	0—25	0—22	0—26	0—23	0—22	0—118
6	0—24	0—21	0—23	0—21	0—17	0—106
7	1—24	1—19	0—23	0—20	0—17	2—103
8	0—23	0—19	0—20	0—18	0—17	0—97
9	0—23	0—18	0—19	0—15	0—17	0—92
10	0—19	0—16	0—19	1—14	0—13	1—81
11	0—19	0—16	0—18	0—11	0—12	0—76

TABLE IV.—ANNUAL AND CUMULATIVE PERCENTAGE INCIDENCE OF RECURRENCE AFTER SUBTOTAL GASTRECTOMY FOR PRIMARY AND SECONDARY DUODENAL ULCER, SAMPLE B, SURGICAL YEARS: 1926–1930

Follow-up year	No. of survivors	Cases followed		Annual incidence of new recurrences			Cumulative incidence of recurrences		
		No.	%	No.	Min. %	Max. %	Min. %	Max. %	Med. %
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
1	180	173	96.1	4	2.2	2.3	2.2	2.3	2.3
2	180	141	78.3	3	1.7	2.1	3.9	4.4	4.2
3	180	133	73.9	1	0.6	0.8	4.5	5.2	4.9
4	180	125	69.4	0	0	0	4.5	5.2	4.9
5	180	118	65.6	0	0	0	4.5	5.2	4.9
6	180	106	58.9	0	0	0	4.5	5.2	4.9
7	180	103	57.2	2	1.1	1.9	5.6	7.1	6.4
8	180	97	53.9	0	0	0	5.6	7.1	6.4
9	180	92	51.1	0	0	0	5.6	7.1	6.4
10	180	81	45.0	1	0.6	1.2	6.2	8.3	7.3
11	180	76	42.2	0	0	0	6.2	8.3	7.3

Column (6)=column (5) divided by column (2); column (7)=column (5) divided by column (3); column (10)=one-half the sum of columns (8) and (9).

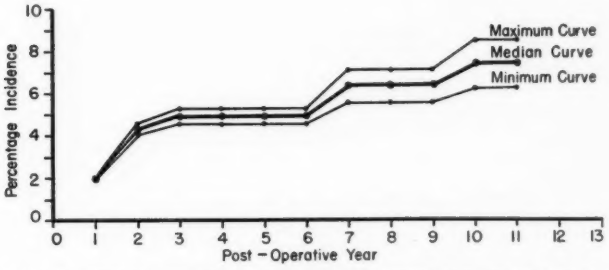

Fig. 2. Same as Figure 1. Sample B covering surgical years 1926–1930. Number of operative survivors 180.

maximum percentage of recurrence (column 9) is calculated similarly from the data of column 7. And finally, the median average of these upper and lower limits is recorded in the last column.

The significance of the foregoing data is best appreciated from their graphic representation. Such plots for the cumulative incidence of recurrence are shown in Figure 1. A similar study on a second sample population (sample B, 1926–1930), which permits of an analysis of results over an 11 year period, is presented in Tables III, IV and Figure 2. A third sample covering the years 1931–1934 (sample C) was available for a 7 year period of study.

TABLE V.—ANNUAL INCIDENCE OF RECURRENCE OF ULCERATION FOLLOWING SUBTOTAL GASTRECTOMY FOR PRIMARY AND SECONDARY DUODENAL ULCER, SAMPLE C, SURGICAL YEARS: 1931–1934

Year of operation	1931	1932	1933	1934	Totals
No. of survivors	39	24	27	10	100
Post-operative year	Summary of annual follow-up by postoperative years No. recurrences—No. cases followed				
1	2—36	0—23	0—27	0—9	2—95
2	0—31	1—22	1—26	0—9	2—88
3	0—26	1—22	1—24	1—9	3—81
4	0—26	0—20	0—24	0—9	0—79
5	0—23	0—16	0—24	0—9	0—72
6	0—19	1—15	0—22	0—7	1—63
7	0—19	0—15	0—19	0—7	0—60

Although this postoperative period is of relatively short duration, the data afford opportunity for comparison with other material of like duration, taken from samples A and B, and so this third sample has also been included in the present study (Tables V and VI, Figure 3).

ANALYSIS OF THE TREND CURVES

In order to comprehend the characteristics of the cumulative trend curves, let us analyze that for sample A in detail (Fig. 1). The maximum and minimum incidence curves both rise with moderate abruptness and then flatten out to form typical plateaux. The two curves have essentially the same shape, the divergence be-

TABLE VI.—ANNUAL AND CUMULATIVE PERCENTAGE INCIDENCE OF RECURRENCE AFTER SUBTOTAL GASTRECTOMY FOR PRIMARY AND SECONDARY DUODENAL ULCER, SAMPLE C, SURGICAL YEARS: 1931–1934

Follow-up year	No. of survivors	Cases followed		Annual incidence of new recurrences			Cumulative incidence of recurrences		
		No.	%	No.	Min. %	Max. %	Min. %	Max. %	Med. %
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
1	100	95	95.0	2	2.0	2.1	2.0	2.1	2.1
2	100	88	88.0	2	2.0	2.3	4.0	4.4	4.2
3	100	81	81.0	3	3.0	3.7	7.0	8.1	7.6
4	100	79	79.0	0	0	0	7.0	8.1	7.6
5	100	72	72.0	0	0	0	7.0	8.1	7.6
6	100	63	63.0	1	1.0	1.6	8.0	9.7	8.9
7	100	60	60.0	0	0	0	8.0	9.7	8.9

Column (6) = column (5) divided by column (2); column (7) = column (5) divided by column (3); column (10) = one-half the sum of columns (8) and (9).

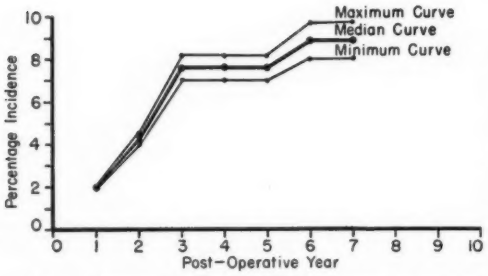

Fig. 3. Same as Figure 1. Sample C covering surgical years 1931–1934. Number of operative survivors 100.

tween them being a reflection of the loss of follow-up patients. Hence, the median curve also possesses the same general form; its plateau starts at the 10th year, which means that all of the recurrences became manifest up to that time and that none were observed during the last 6 years of follow-up. This total median incidence of recurrence is 9.6 per cent, and of this total about two-thirds (6.5%) occurred during the first 5 years after operation and one-third (3.1%) during the second 5 year postoperative period. Similar characterizations might be made for any other grouping of years (e.g., 4, 8, 12, and 16) but the 5 year intervals are those in common use.

The curves of sample B (Fig. 2) possess essentially the same characteristics, although a continuation of only 1 year beyond the 10th is insufficient to establish the existence of a plateau. The total median incidence of recurrence through the 10th year is 7.3 per cent; the proportion of these recurrences in the first 5 year period is again about two-thirds (4.9 per cent) and for the second such period it is one-third (2.4%). It will be noted that the divergence between the maximum and minimum curves at the 10th year is appreciably less for sample B than for sample A (2.1% as compared with 4.0%) thus making the estimate of "true" incidence in the former more reliable than in the latter. Obviously, this difference in spread for the two samples is a reflection only of the difference in their relative completeness of follow-up. As for sample C (Fig. 3) analysis of these characteristics is as yet impossible because of the limited duration of the experience.

In order to compare the results from these 3 samples more effectively, their median curves are presented together in Figure 4. The general similarity in shape is apparent, although certainty on this score must await the passage of sufficient time (at least 13 or 14 years of study in each instance) to insure the existence of the plateau. The question naturally arises: is the difference in height of these curves indicative of a significant difference in their respective incidences of recurrence, or is it merely a reflection of random sampling? (For an amplification of this concept, see the "Evaluation of Study"). For instance, the 10 year incidence of recurrence for samples A and B is 9.6 and 7.3 per cent respectively, with a difference of 2.3 per cent between them. To determine whether this difference is statistically significant, we may apply the statistical test generally used in such circumstances (see the Appendix). The result indicates that this difference is not significant and arises only by reason of the variation which may be expected from sample to sample of the same population. A similar test applied to the cumulative 5 year incidence from these two samples yields a difference of 1.6 per cent (6.5–4.9) which is likewise not significant by this statistical criterion. The third sample, which has been under observation for only 7 years, yields a 5 year incidence of recurrence of 7.6 per cent, but the difference between this and 4.9 per cent for sample B is also not significant. In this way we have established partially the consistency of these 3 sets of data, or their statistical homogeneity.

EVALUATION OF STUDY

Our procedure for evaluating the therapeutic end-results of surgery for peptic ulcer involves certain definite departures from previous methods. The principles upon which our procedure has been based are as follows: (1) Rigorous adherence to a study of each case at regular time intervals (i.e., a record of the year-by-year destiny of each patient) is essential. This must be based on a carefully defined criterion of "failure." (2) Such periodic follow-up must be continued as long as the patient lives. (3) In grouping cases for statistical analysis, a limiting minimum duration of fol-

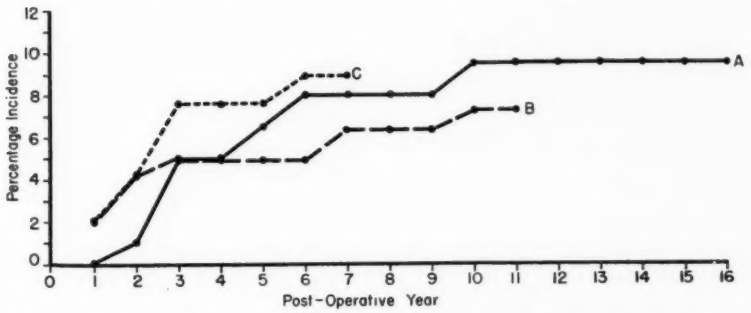

Fig. 4. Median trend curves for the cumulative incidence of recurrence of ulceration following subtotal gastrectomy for duodenal ulcer. *A*, Surgical years, 1923–1925; *B*, 1926–1930; *C*, 1931–1934.

low-up must be adopted for the study, and no patient who has been followed for less than this minimum period may be included in the corresponding population sample. Of course, if the total number of cases is large enough and the period of observation long enough, the entire group of cases may be split into two or more subgroups of different limiting durations, and these can be analyzed independently of each other. (4) The measure of failure is calculated in three ways: (a) the *minimum possible incidence*, based on the total number of operative survivors which might potentially have been followed for the indicated postoperative time; (b) the *maximum possible incidence*, based on the total number of cases which actually were followed in the course of the indicated postoperative year; and (c) the *median incidence*, which is an average of the maximum and minimum possibilities. (5) The year-by-year cumulative trend curve for the (median) measure of incidence is studied with a view to establishing a patient's chances of recurrence at any time following operation. (6) Finally, from such a trend curve, it is possible to set up an *index of failure* of the operation in question. This is given by the median percentage incidence of recurrence at the plateau, and it represents the maximum chance of recurrence, irrespective of time, to be expected for the conditions which characterize the group of cases under analysis.

Such an *index of failure* constitutes a statistical measure of the efficacy of the operation. It is a single number which represents the entire mass of data in respect to the therapy—in short, a "statistic." This commits us to a statistic which measures "failure" rather than "success"; although the two appear to be complementary they are not entirely so, for an unsuccessful case always remains unsuccessful, but a successful one may become a failure at any time. Studies involving the index of failure are subject to breakdowns according to different variables (age, acidity, obstruction, etc.), and appropriate tests of statistical significance must be applied in these situations wherever they are required. In the consideration of any new candidate for surgery, it must be remembered that his risk of recurrence may be influenced by the special characteristics which his case presents, and that the various factors which may contribute to the recurrence of the disease are of the utmost importance in this regard. Such breakdowns of the data are not illustrated here, but they will be presented in a subsequent report on an actual experience at this hospital.

In searching the literature dealing with the end-results of ulcer therapy, we were impressed by the fact that in years past almost no attention was given to the basic problems of statistical methodology. The first such study to indicate an awareness of these problems was published by St. John (3) in 1930 and this was followed 9 years later by a detailed development of his earlier ideas (4). Apart from the contributions of this group of workers we know of no other publications which manifest any consciousness of the com-

plexity of the biometrical problem facing the clinical investigator of ulcer therapy. A recent paper by Campbell called the attention of the surgical profession to the problem of random sampling as it applies to the interpretation of postoperative mortality data in general, and it emphasized the importance of tests of significance in the comparison of "percentages" based on different groups of cases—but it gave no consideration to the statistical evaluation of therapeutic end-results. When we first set out to develop a statistical technique for our own use, we were concerned with discovering the ultimate success or failure of an operation for peptic ulcer and *how long we must continue to observe our cases after operation in order to determine this factor*. In scrutinizing the procedures previously followed for determining the end-results of treatment, we could find none which afforded this information to our satisfaction. Thus, the use of an *average period of follow-up* for a group of patients may lead to a numerically different picture from that which would be obtained if every individual in the group had been studied for the same length of time. Furthermore, the use of any arbitrarily limited period of observation to establish a measure of therapeutic success (e.g., a 5 year follow-up period) cannot be accepted until it has been validated by an independent statistical study of its merits, and we were aware of no such study. Hence, we were under the necessity of devising a statistical procedure which would fulfill the requirements of this problem as we perceived them. The result is the method described in this report.

Let us consider the limitations of this new statistical method. Some of these limitations are inherent in any statistical procedure for the study of therapeutic results, especially of a disease like peptic ulcer; others may be specific to the present method alone, and these should be clearly recognized.

1. The reliability of the raw data (i.e., of the characteristics of the clinical material chosen for analysis) is always open to question. Apart from the personal equation of the investigator, the descriptive nature of the phenomena sometimes makes a clear-cut classification impossible. For instance, a case of painless bleeding following subtotal gastrectomy may result from a recurrent ulceration, an erosion, or an inflammatory duodenitis, gastritis, or jejunitis. The interpretation of such a case, therefore, must always be open to some uncertainty.

2. The loss of follow-up material may prove to be a serious handicap to any statistical study related to peptic ulcer. To cope with this problem it is necessary, first of all, that every effort be made to develop a follow-up organization of the utmost efficiency. This requires a specialized personnel, dedicated to the task of tracing a patient by every possible means. Concerning the residue of unfollowed cases, one may assume that their results on the average are, or are not, essentially different from those for the cases actually observed, but one or the other of these assumptions must be made in order to carry on with the statistical study. Limiting the study to the cases actually observed and disregarding the unfollowed cases involve the tacit assumption that the latter are statistically homogeneous with the followed group. Some clinicians may prefer to perform no statistical studies whatever, rather than commit themselves to any such assumption. We feel that their attitude is unwarranted in that it is purely destructive and contributes nothing to the eventual solution of any problem requiring investigation. On the contrary, it is better to perform a study of this kind with all its limitations, provided only that the source of the limitation never be lost from sight. A real solution of the problems created by the unfollowed case can come about in only one way, if at all, under present working conditions—that is by means of a central agency to which all clinics may send records of patients who had previously been treated at other institutions. The data so collected should be tabulated according to a generally accepted method and some machinery be established for making the results immediately available to the hospital where each patient was originally treated. After 20 years of inconclusive debate about the results of ulcer therapy, this seems to be the most practical solution to the problem presented by the unfollowed cases.

In the absence of such a solution, we have assumed in this particular study that the un-

followed cases were statistically homogeneous with those which were followed—for reasons which we defined clearly. In addition, however, we set up a dual measure of percentage incidence, in order to minimize any weakness inherent in this assumption. That is, we calculated both maximum and minimum estimates of this incidence, based on the total potential and actual follow-ups of the cases, and we cited reasons for believing that the true value lies between these two extremes. For convenience, in comparing different groups of data, we have employed the median average of these two limiting values as the most probable index of failure.

3. Assuming that neither of the foregoing limitations offers a serious obstacle to a statistical investigation, we next are confronted with the following question. Given 2 independent sets of observations or results by the same operation, which yield manifestly different total incidences of recurrence, how can we be sure that their difference is significant according to the usual statistical criteria? Before any consideration is given to possible reasons for a difference in results between two sets of data (such as surgical technique, or racial and economic characteristics of the patients), it must be established that the difference cannot be due solely to random sampling—in other words, that the difference is larger than is likely to occur between 2 groups of cases drawn from a single large uniform population. For this purpose we have employed the accepted statistical technique of a significance test based on the ratio of a difference between 2 means (or percentages) to its own standard deviation—sometimes called the *significance ratio* (See Appendix). If the data in question be subjected to this type of statistical analysis and it develops that the difference is *not significant*, then it follows that the difference between the 2 sets of data, *in all probability*, is a result only of the accidental variation in biological material which arises in the choosing of sample groups from a large parent population. In the several population samples used here to illustrate our technique, the differences both for 5 year and for 10 year follow-ups clearly had no statistical significance. On the other hand, had the difference in these incidences of recurrence proved to be significant, then it would be incumbent upon us to seek the factors responsible for the dissimilarities.

Clinical investigators are generally unaware of (or indifferent to) the concept of *random sampling*, and the errors which may result from its neglect. This statistical concept is simple and requires no special mathematical knowledge for its comprehension. Let us assume, for instance, that there exists a recurrence index which truly characterizes the surgical procedure under discussion, as it might be applied in *all* cases—past, present, and future. Such a group of cases constitutes a theoretical "universal population" of all cases subjected to this operation. If, now, we choose "samples" of this "universe" (i.e., small groups of the cases which constitute the universal population) we will find that the recurrence index for any such sample may differ materially from that for the other samples as well as from that for the entire population. If any such smaller group of cases is chosen entirely at random, so that no major factor differentiates it from any other sample of the universal population, then the differences among these several indices may be expected to conform to certain statistical laws. If the difference between any two such indices is greater than may be expected from these mathematical relationships, then we say that the two groups of cases are significantly different in that some factor or group of factors is present in one situation and absent from the other. Such use of these mathematical relations constitutes the test of significance of a difference between 2 groups of data, already referred to. It must be noted that 2 samples from the same population may differ materially in their recurrence index, but their difference may not be significant in the statistical sense. This being the case, the clinician must be very wary about drawing conclusions from such comparisons, unless he is quite certain that the difference has not arisen purely by reason of random sampling. Note also that the result of a significance test may be indecisive, in that it fails to indicate clearly that the difference between two values is, or is not, significant. This may happen because of the size of the

difference relative to its standard deviation, i.e., the probability ratio lies between 1 and 2.6 (see Appendix).

4. In connection with the preceding, there arises a question concerning the number of cases in each set of data and their adequacy for such a comparison. If the difference between the percentage incidences for 2 groups of cases is clearly significant (or not significant) with a high degree of probability, then the number of cases may be considered adequate, even when the group is as small as 25. If, on the other hand, the difference is of indecisive significance, increasing the sizes of the samples may serve to eliminate the uncertainty on this score. Clinicians frequently ask this question in another form: "Having conducted a study on a single group of cases and having arrived at an index of mortality or of operative success, how can one be sure that the number of cases in the group is sufficient for drawing valid inferences?" But what do clinical investigators expect from their studies in the way of "inferences"? Such expectations are twofold: (a) an evaluation of their therapeutic results relative to a second set of data—in other words, a comparison of 2 groups of results; (b) a measure of such efficacy as may be expected for a similar group of data not yet treated—in other words, prediction of the degree of success which may be anticipated in the future, on the basis of an adequate past experience or trial sample.

For the first of these expectations, one can say that if the test for significance of the difference between the 2 sets of data is clearly decisive with a high degree of probability (taking suitable account of "small number theory") then the number of cases is satisfactory. We have previously referred to the use of the *standard deviation* of a mean value or a percentage as the basis for tests of statistical significance. The magnitude of this statistical criterion of *scatter* of a group of data is determined by the size of the sample population as well as by the mean or percentage incidence value itself. Hence, if we are concerned with the therapeutic indices of 2 sets of data, and we desire to know whether these sets contain a sufficient number of cases for the purpose of comparing them, we must first apply the significance test to the difference between the 2 indices. If the result be *clearly decisive*, either for significance or for nonsignificance, then we may say that the number of cases is probably adequate for the purpose in hand. If, however, the result proves to be indecisive, then we are under the necessity of gathering more data before any conclusion can be drawn. The resultant increase in the total number of cases will, in general, decrease the standard deviation of the mean or percentage, and thereby increase the likelihood of our arriving at a decisive conclusion from the test for statistical significance.

The second of these expectations (prediction) presents a more difficult problem. It is obvious that the larger the trial sample the more reliable will be the statistical inference drawn from it. Nevertheless, under certain circumstances even samples as small as 25 cases may afford a basis for prediction of considerable validity. Whether this number is adequate, however, can be learned only after several such trial groups have been compared in order to learn something about the variation from sample to sample. Furthermore, it must be remembered that prediction is always fraught with uncertainty, because it presumes that the general characteristics of the group of cases for which prediction is being made do not differ significantly from those of the trial groups on which the therapeutic index was determined—in other words, that they are all random samples of the same universal population. Without this homogeneity, it is obvious, results on the one group cannot be predicted from those on the other. Granted this comparability of the 2 groups, however, we may then expect that the index of our predicted group will agree with that for the trial group only as well as any 2 trial groups may agree with each other. We must not lose sight of the uncertainties arising from random sampling, and we must remember that a future result may differ from a predicted one by as much as the laws of chance, or random sampling, allow for. Hence, the investigator must learn that clinically identical material may yet differ in regard to surgical or therapeutic end-results by considerable amounts. For practical purposes, he is under the necessity of

making such predictions for the guidance of himself and his colleagues, but he must be constantly aware of the possibility that his prediction may fall down. In other words, he is taking chances in the statistical as well as the vulgar sense.

What can we say about the number of cases required to establish a valid index for a group of data, without reference to any other group —past, present or future. The consideration of any isolated group of cases in this way is always valid, irrespective of the number of cases, *provided that the index so calculated is accepted only to describe this one group of cases.* This means that the clinician does not intend to use this index as a reflection of any other clinical experience whatsoever, but only for the purpose of description, and here the question of statistical validity does not ordinarily enter. However, just as soon as the index for this group be compared with that for another experience, or be used for predicting the risk or chances of success in a group of cases about to be treated, then we are confronted with a wholly different situation—one in which the process of inference and the question of statistical validity must always be uppermost in the mind of the investigator.

SUMMARY

This report is introduced with a review of the procedures which have been employed by clinical investigators for evaluating the results of their therapeutic (chiefly surgical) methods for peptic ulcer. Following a discussion of the statistical weaknesses of these procedures and of certain fundamental conditions which must be adhered to in order to insure statistical validity to any such procedure, we have presented a statistical procedure of our own which conforms to these requirements. For this purpose, and in order to cope with the problem arising from unfollowed cases, we have adopted the following premise: that the incidence of failure among the group of unfollowed patients is no greater than among the observed group, and it may be even less. We believe that this premise is valid for ulcer surgery with a high degree of probability, but if future evidence necessitates its modification we are prepared to change it according to the facts.

The new method yields maximum and minimum estimates of the cumulative trend curve (by years) for the percentage incidence of post-therapeutic recurrence of ulceration. From such a pair of graphs, we calculate a median average curve which we believe to have greater validity than either of the limiting curves. In order to facilitate description of this statistical technique we have employed 3 sets of data from the records of the Mount Sinai Hospital, for cases of duodenal ulcer which had been subjected to subtotal gastrectomy during the years 1923–1934. The statistical concept of random variation is discussed, particularly in relation to the variations among these 3 series of cases and to the number of patients which may be considered adequate for such a study. The several median trend curves give evidence for the existence of a plateau beyond the 10th year—which means that, in all likelihood, any patient operated upon will develop a recurrence either during the first 10 postoperative years or not at all. From these data, the average total incidence of recurrence following subtotal gastrectomy for duodenal ulcer is in the neighborhood of 9 per cent.

Although various therapeutic measures have been devised to control or abate ulcer activity, none can assure a certain cure of the disease. Moreover, since the results with these therapies may be influenced by a multiplicity of factors, the quantitative measurement of their efficacies resolves itself into a statistical problem. This implies the use of a logical, well conceived technique, which fulfills the requirements of statistical theory. The failure to recognize this basic idea of methodology has contributed in a large measure to the confusion, which has now existed for more than two decades, concerning the results with certain surgical therapies for peptic ulcer. Unless the basic importance of "statistical methodology" is recognized, there is no reason to expect future efforts in this problem to be any more conclusive than those of the past.

A detailed discussion of these data from the clinical point of view, including the characteristics of the material, the factors which influence the results of operation at this hospital, and the implication of our statistical conclusions, will be presented in a later report.

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APPENDIX

The significance test used in this report is the elementary one, based on the "probability ratio." For this particular situation, let:

p_1 = the fractional 10 year incidence of recurrence in, say, sample A (i.e., the percentage incidence divided by 100).

p_2 = the corresponding value for sample B.

N_1 = the number of cases in sample A, which is taken as the mean of the original number of operative survivors and the number of patients seen at follow-up in the tenth year.

N_2 = the corresponding value for sample B.

Then $p_1 - p_2$ = the difference in fractional incidence of recurrence between the two samples (i.e., the value whose significance is to be tested).

s_1 = the standard deviation of $p_1 = \sqrt{\frac{p_1(1-p_1)}{N_1}}$

s_2 = the standard deviation of $p_2 = \sqrt{\frac{p_2(1-p_2)}{N_2}}$

and the probability ratio is given by

$$PR = \frac{(p_1 - p_2)}{\sqrt{s_1^2 + s_2^2}}$$

If $PR = 1$, it means that the difference $(p_1 - p_2)$ may be the result of random sampling 317 times in every 1000 experiences, and therefore that it is significant of some particular influence other than random sampling 683 times in every 1000. If $PR = 2$, the chances that the difference is "significant" are 955 in 1000; and if $PR = 3$, the probability of significance is around 997 in 1000. In order for the probability of significance to be 990 in 1000 or 99 per cent, PR must be 2.6. The latter value for PR is the one accepted as critical in the present investigation; if any pair of percentage-recurrence values yield a PR value of 2.6 or greater, the difference between them is said to be "significant at the 1 per cent level of probability." Nonsignificance is indicated by $PR = 1$ or less, and a value between 1 and 2.6 may be considered indecisive. There is available a more refined procedure, based on the estimation of the standard deviation of the parent population from which samples A and B are supposed to have been drawn, but such refinement is hardly warranted for our present purpose.

The following table contains a summary of the several significance tests referred to in the text; the subscripts indicate the duration of follow-up in each case.

Samples	$p_1 - p_2$	N_1	N_2	PR	Significance
A_{10} and B_{10}	.096—.073=.023	71	131	0.56	None
A_5 and B_5	.065—.049=.016	77	149	0.48	None
C_5 and B_5	.076—.049=.027	86	149	0.82	None
C_5 and A_5	.076—.065=.011	86	77	0.28	None

THE EFFECT OF THORACIC DUCT DRAINAGE AND HEMORRHAGE ON THE BLOOD AND LYMPH

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AMPLE investigation has been made of the changes in the blood caused by the redistribution of fluid and protein in the acute phase of hemorrhage. Recent advances in the physiology of hemorrhage resulted in the suggestion by some observers (3, 4) that the lymph might be an important factor for the replacement in the blood of essential elements lost by bleeding. However, no direct studies on both the blood and lymph have been reported since Haynes's observation on the concentration of proteins in blood and peripheral lymph during hemorrhage.

In the present investigation, the effect on the specific gravity of the blood and lymph, of acute hemorrhage, of continuous lymph drainage, and of both acute hemorrhage and continuous lymph drainage was studied.

The animals were divided into 3 groups and were prepared in the following manner. Dogs whose average weight ranged from 13 to 16 kilograms were anesthetized by an intravenous injection of 1 cubic centimeter of 3 per cent pentobarbital-sodium per kilogram of body weight. Endotracheal artificial respiration was administered by a differential insufflation machine. Kymographic tracings of arterial pressure were taken from the femoral artery.

The dogs of group 1 were subjected to drainage of lymph by cannulation of the thoracic duct which was exposed in the neck and disconnected from the subclavian vein at their point of junction. The lymph was drained continuously and collected in citrated tubes at 20 minute intervals for a period of 3 hours. In addition also at 20 minute intervals, 45 cubic centimeters of blood was drawn from the femoral artery. The dogs of groups II and III served as controls. The animals of group II were subjected only to repeated bleedings and consisted of the withdrawal of 45 centimeters of blood at 20 minute intervals. The third group of animals was subjected to the continuous drainage of lymph without hemorrhage.

The following determinations were made. The specific gravity of the blood, the plasma, and the lymph was determined by the falling drop method of Barbour and Hamilton (8). The hematocrit cell volume was measured in Wintrobe tubes. The changes in the density of the lymph, the blood, and the hematocrit values after the injection of nembutal were regarded as the initial values in contradistinction to the normal preanesthetic values.

RESULTS

Group I. Rapid progressive hemorrhage and continuous lymph drainage. Ten dogs, each with an approximate weight of 16 kilograms, were subjected to an average loss of 21 per cent of their total blood volume and a loss of lymph equivalent to 18 per cent of the total amount of blood withdrawn.

Lymph obtained by continuous drainage during the experimental period averaged 89 cubic centimeters. The smallest amount obtained was 58 cubic centimeters, the greatest 120 cubic centimeters. In 7 dogs, the specific gravity of the lymph increased progressively over its initial value (1.0187, average) during the course of the repeated bleedings. The increase averaged 0.0057, so that in some cases, the final specific gravity of the plasma and lymph was almost equal. In the 3 other dogs, the specific gravity of the lymph fell below its initial value. The fall averaged 0.0018.

The specific gravity of the plasma tended to decrease progressively, but for the exception of one or two small increases which corresponded to similar changes in the density of the

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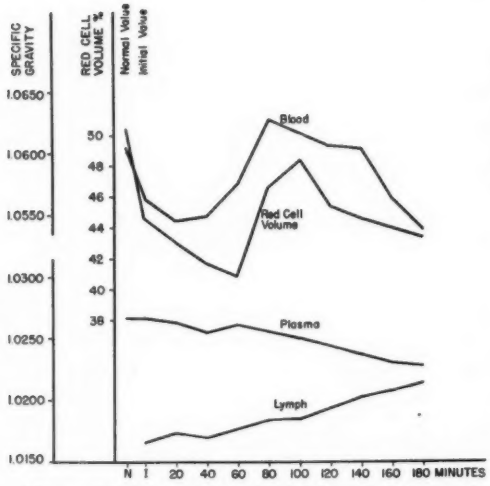

Fig. 1. Changes in the blood and lymph during rapid progressive hemorrhage and continuous thoracic duct drainage. Group 1, experiment 8. The initial specific gravity of the blood is markedly reduced below the normal value as a result of the injection of nembutal (engorgement of the spleen). After the first bleeding, there is a further small decline in specific gravity of the blood. After the third bleeding, the specific gravity of the blood increased above its normal value (contraction of the spleen). Thereafter with subsequent bleedings, the specific gravity of the blood fell almost progressively. The changes in the hematocrit values paralleled those of the blood. The specific gravity of the plasma declined progressively except for a brief period when it increased slightly coincident with the increase in the specific gravity of the blood. The specific gravity of the lymph increased markedly and almost equalled the specific gravity of the plasma.

whole blood. The initial specific gravity of the plasma was 1.0272 (average) and its maximum fall was 0.0063 (average).

The specific gravity of the whole blood at the end of the experiment fell 0.0026 (average) below its initial value (1.0553, average). The decline in specific gravity of the whole blood was usually progressive for the first three bleedings and was followed by a temporary sharp increase in density after which there was a continuous fall in specific gravity until the end of the experiment.

Corresponding with the increase in the specific gravity of the blood, the hematocrit values (39.5 volumes per cent, average initial value) also increased 5.3 volumes per cent (average). At the end of the experiment, the hematocrit cell volume was reduced 1.8 volumes per cent (average) below its initial value.

The initial blood pressure (123 mms. Hg. average) fell approximately 4 millimeters-mercury with each bleeding and recovery usually took place within 5 minutes. After the sixth withdrawal of blood, the arterial pressure fell to 80 millimeters mercury (average) and recovery to the latter level in the subsequent bleedings required about 12 minutes. In 4 of the dogs from whom the greatest amount of lymph was obtained by drainage, the blood pressure fell to 20 millimeters mercury (average) after the sixth bleeding. In the others, the blood pressure varied from 63 to 76 millimeters mercury.

Group II. Hemorrhage experiments in the intact animals. Ten dogs with an average weight of 18 kilograms were subjected to a loss of 24 per cent of their total blood volume by repeated bleedings.

The specific gravity of the plasma (1.0262 average) fell 0.0038 (average) as a result of the bleedings. The specific gravity of the whole blood (1.0595 average) and the hematocrit cell volume (39.7 volumes per cent average), as in the previous group, increased for a brief period and then fell progressively to 1.0552 and 36.3 volumes per cent (average) at the end of the experiment. The initial blood pressure, approximately 118 millimeters mercury (average), declined with each withdrawal of blood; recovery of blood pressure was similar in character to the recovery change in the previous group and at the end of the experiment ranged between 70 to 76 millimeters mercury.

Group III. The effect of continuous lymph drainage on the blood. Five dogs with an average weight of 15.8 kilograms were subjected to continuous thoracic duct drainage as a result of which an average of 93 cubic centimeters of lymph was obtained from each animal. At 20 minute intervals, 5 cubic centimeters of blood was drawn to determine changes in the hematocrit cell volume and in the density of the blood. In this way, only 0.03 per cent of the blood volume was lost. The initial specific gravity of the lymph averaged 1.0198 and all determinations varied no more than 0.0011 from this value. The specific gravity of the whole blood (1.0579 average) varied 0.0010 above or below the initial value, while that of the plasma (1.0291 average) likewise varied no

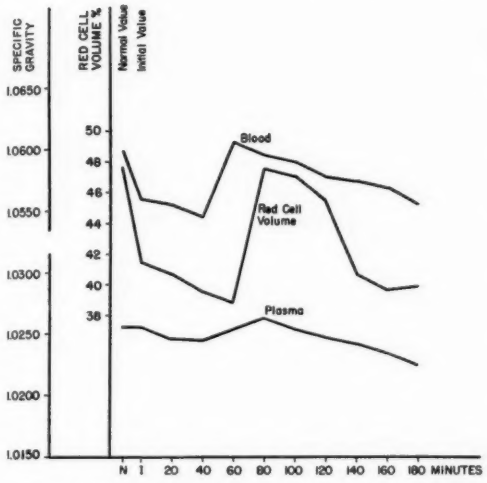

Fig. 2. Changes in the blood during rapid progressive hemorrhage. Control group II, experiment 3. After the injection of nembutal, the initial specific gravity of the blood fell below the normal preanesthetic level. With the first 2 bleedings, the specific gravity of the blood continued to fall. This was followed by a sharp rise in specific gravity of the blood, after which with subsequent bleedings, the fall in specific gravity was progressive but small. The hematocrit values followed the same trend as the blood. The specific gravity of the plasma also exhibited similar changes as that shown by the blood.

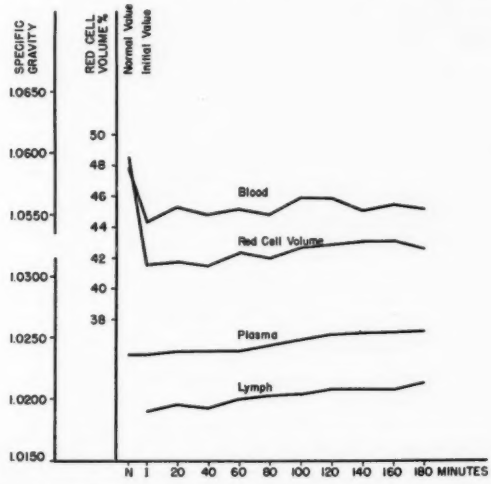

Fig. 3. Changes in the blood and lymph during continuous thoracic duct drainage. Control group III, experiment 2. Other than the marked fall in specific gravity of the blood due to the anesthetic agent, the changes in specific gravity of the blood during the course of the experiment were not marked. The hematocrit values increased slightly in concentration toward the end of the experiment. The specific gravity of the plasma also increased slightly. There was, in addition, a small increase in specific gravity of the lymph during the course of continuous lymph drainage.

more than 0.0017 throughout the experimental period. The hematocrit cell volume did not exceed its initial value of 40.2 volumes per cent (average) by more than 0.9 volumes per cent (average). There were no significant changes in blood pressure.

EVALUATION OF STUDY

Readjustments in the specific gravity of the whole blood, the plasma, and the lymph followed after each bleeding and resulted in changes which indicated dilution or concentration depending on the rate of translocation of tissue fluids from the extravascular spaces. In all cases, these variations could be accounted for on a physiological basis when the hematocrit cell volume and the specific gravity of the body fluids were correlated.

In 70 per cent of the dogs in group I, the specific gravity of the lymph exhibited a trend toward concentration, while the plasma tended toward progressive dilution during hemorrhage. The increase in the density of the lymph and the decrease in the density of the plasma may be accounted for on the basis of withdrawal of fluid from the tissue spaces and its direct entry into the blood. As a result, the concentration of the remaining constituents of the tissue fluid increased and drained into the lymphatic capillaries whose endothelium is known to be highly permeable (5). The validity of this concept appeared to be substantiated experimentally since the dilution effects of bleeding were generally more pronounced in the lymphaticostomized dogs of group I than in the intact normal animals subjected to hemorrhage only. It was obvious therefore that in the latter group of normal dogs, the thoracic lymph duct supplied significant amounts of fluid directly to the blood during the process of hemorrhage.

The concentration of protein in the thoracic lymph duct as computed from the specific gravity values increased as a result of hemorrhage from an approximate initial value of 4.0 grams to 6.50 grams. If the average rate of

lymph flow from the thoracic duct were estimated at 31 cubic centimeters per hour, there could be a maintained return to the blood by this route of approximately 1 to 2½ grams of protein per hour. Thus a loss of 27 grams of protein as contained in 360 cubic centimeters of blood might be restored within 27 hours by this lymphatic channel. Since the loss of protein and fluid by continuous lymph drainage alone was small, it was plain why this did not markedly affect the specific gravity of the blood or plasma, while hemorrhage combined with lymphaticostomy was effective in changing significantly the density of the blood and resulted even in the precipitation of shock in some cases.

The other phases of hemorrhage involving changes in blood pressure, hematocrit cell volume, blood and plasma specific gravity have been adequately investigated by Schlossberg and Sawyer, and Adolph *et al.* (2), and reaffirmed in this study. Reductions in blood volume of less than 30 per cent, as in these experiments, did not impair the activity and response of the sympathetic nervous system which maintained blood pressure above shock levels and thus influenced the transfer of tissue fluids to the blood in accordance with the Starling concept. The changes in hematocrit cell volume and whole blood specific gravity have already been shown to be due to engorgement of the spleen in association with the anesthetic agent (1), after which followed a rapid emptying of the spleen mediated by the sympathetic nervous system and activated by the process of hemorrhage. Plasma dilution in hemorrhage is now a well recognized fact which has been demonstrated by many observers (2).

SUMMARY

The effect of hemorrhage on the blood and lymph was partitioned and studied. It was found that coincident with blood plasma dilution, there was usually a concentration of the density of the lymph in dogs subjected to both the loss of blood and lymph. In the animals without lymphaticostomy, the changes in the specific gravity of the blood and plasma during the bleedings were not as marked as in the previous group. Continuous lymph drainage for a 3 hour period without hemorrhage failed to affect significantly the specific gravity of the blood.

The lymph served an important rôle in the compensatory mechanism of hemorrhage not only as a pathway for fluid but also as a source of protein replacement.

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CONGENITAL NARROWING OF THE LUMBOSACRAL SPACE

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IN x-ray interpretations of the painful low back, increasingly greater emphasis is being placed upon the finding of a narrowed lumbosacral intervertebral space. For the past several years, it has been stressed that such a narrowing usually resulted from a herniation of the nucleus pulposus. It was reasoned that only a displacement backward of the nucleus pulposus could account for the thinning of the intervertebral disc so often encountered at the lumbosacral angle. The concept was new, the explanation simple, and in many patients the condition was erroneously diagnosed as a herniated nucleus on the prima facie evidence of a thin disc. However, in 1938, Clarkson and Barker wrote that "a proven rupture of the intervertebral disc explains the narrow joint in a certain number of patients, but a satisfactory explanation for the narrowed lumbosacral space seen in many individuals never has been given." And more recently, in Ellis's monograph on the low back, the statement is made that a narrowing of the intervertebral space at the site of a ruptured disc occurs in only a small percentage of cases. It has been shown that narrowing often occurs at a different level than the site of retropulsion as found at operation.

Another explanation for the narrowing of the lumbosacral intervertebral space is the disintegration of the annulus fibrosis and nuclear material incidental to the wear and tear of life. The concept is particularly reasonable since such narrowing is seen in those backs which, through structural anomalies, are mechanically weaker than normal. Incomplete sacralization, asymmetrical facets, an acute lumbosacral angle, defects in the posterior elements, all make a relatively vulnerable joint unstable. Lipping and sclerosis of the vertebral bodies or zygoapophyseal joints often accompany these structural anomalies, indicating the unusual amount of stress and strain which may occur in this weakened area. It would seem logical, then, that the wear and tear which can induce these arthritic changes can also produce gradual destruction and narrowing of the intervertebral disc. Just how the disc degenerates is a matter of speculation. Many small herniations through the cartilaginous plates into the bodies of the inferior and superior vertebrae may occur, with associated inspissation and desiccation of the nuclear material. When the nuclear contents escape through the multiple small defects into the spongiosa of the vertebral bodies, narrowing would occur without signs of nerve root irritation. Such cases would reveal narrowing of the intervertebral space without the presence of a well demarcated Schmorl's node on the roentgenogram. Beadle, at least, is of the opinion that such is the true pathogenesis of the narrowed intervertebral disc.

Pathological studies by most investigators, however, have disclosed interruptions in the continuity of the cartilaginous end plates to be single rather than multiple, with the escape of enough nuclear material to produce an easily discernible Schmorl's node. Such studies would tend to discredit the theory of the narrowing being secondary to the multiple fissures of the end plates, and some further explanation must be advanced. It is our belief that a congenital narrowing of the disc occurs more frequently than is commonly accepted.

The incidence of congenital narrowing of the intervertebral space has not been great in our experience but has occurred often enough to make us aware that serious diagnostic errors can be made. This is in agreement with Willis, whose classical work in this field stands practically alone. On the other hand, Mixter is of the opinion that congenital narrowing is of rather frequent occurrence. We recently reviewed the x-ray films of the lumbosacral junction in three hundred children between the ages of 5 and 15 years, discarding all cases

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in which there was any evidence of a fracture, infection, trauma, or whose roentgenograms were not technically satisfactory. It was our opinion that any narrowing occurring in this age group must be of congenital origin, since destructive changes incident to trauma would be less likely encountered in children. Review of these x-ray films disclosed three cases, Figures 13 and 14, of narrowing other than that resulting from such obvious pathological processes as tuberculosis, sclerosis, osteochondritis, or osteomyelitis. Roentgenograms of these cases revealed associated anomalies, lumbarization or sacralization being present in all instances. Williams also examined a like number of films and found only one which had a narrowing which could be considered congenital in origin. Williams states, however, that there is one type of congenital spine which presents a sacralization of the 5th lumbar vertebra. The lumbosacral disc in such a case shows the narrow character of the sacral intervertebral disc. Confusion may arise when there is partial lumbarization of the first sacral segment. The intervertebral disc between the 1st and 2nd sacral vertebrae retains its narrow character and from a lateral view may be mistaken for the lumbosacral disc. Willis emphasized this observation in saying, "Still a third manifestation of partial sacralization of a last lumbar segment and one that is often wrongly interpreted as a pathological lesion is narrowing of the lumbosacral disc. In anomalous sacralization, the vertical diameter of the disc may vary between the usual thick lumbosacral type and that of the thin sacral disc. A thin disc is in itself no part whatever of a destructive or pathological lesion. Particularly if such a disc is associated with enlarged transverse processes or other evidence of anomalous sacralization, as are most of these shown in clinical discussions, such pathological interpretation must be received with considerable reservation." Hodges and Peck have written, "The finding of a narrow disc is undoubtedly to be expected in the case of patients showing evidence of bilateral or even unilateral fusion of the 5th lumbar vertebra with the sacral mass."

Our small series is essentially in agreement with the findings of others, that such congenital narrowing exists only in the presence of other structural anomalies at the tension point of the spine. It would seem then, that a narrowing of the lumbosacral disc as a congenital anomaly exists frequently enough to be of diagnostic significance.

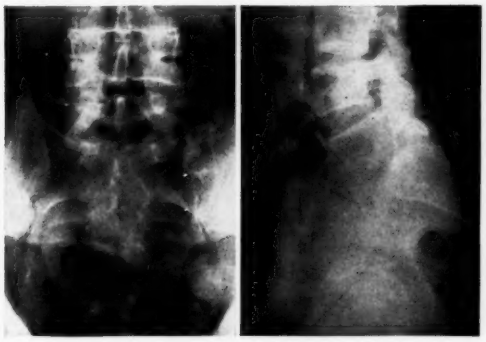
In a short period of time, we have seen x-ray films of several adults whose lumbosacral space has been appreciably narrowed. These were cases of low back pain without sciatica, whose history and findings were not suggestive of a ruptured disc.

CASE REPORTS

CASE 1. M. H., white female, aged 31 years, was first seen in out-patient dispensary, complaining of pain over the low back and coccyx of 2 weeks' duration. The onset of pain dated from a recent fall out of a swing, the patient landing on her buttocks. Her greatest pain was localized over the coccyx and lower sacrum and at no time had there been any radiation of pain down either leg or onto the abdomen. Rectal examination revealed the coccyx to be normal in contour and without angulation, but movement of the coccyx between the examining fingers produced exquisite pain. Examination of the low back revealed normal range of motion without muscle spasm or tenderness. Leg signs were normal, knee and ankle reflexes were intact, and there were no sensory or motor changes in either extremity. The diagnosis was tear of the sacracoccygeal ligaments. She was placed upon sitz baths and local heat under which she made a satisfactory response. X-ray films (Figs. 1 and 2), taken of the lumbosacral region, revealed an appreciably narrowed interspace at lumbosacral junction with lumbarization of 1st sacral vertebra.

CASE 2. W. E., negro male, aged 27 years, was seen in the out-patient dispensary because of low back pain of 1 month's duration. He ascribed the onset of the pain to lifting of some heavy rocks at that time. There was no history of radiation of pain down either leg or onto the abdomen. Examination of the low back revealed marked muscle spasm of the erector spinae on both sides at the lumbar level. There was an exaggeration of the normal lumbar lordosis. All back motions were sharply restricted. There was generalized tenderness over the zygoapophyseal joints, bilateral, at the lower lumbar levels and over the sacrum. Straight leg raising was limited to 110 degrees on both sides. Babinski, ankle and knee reflexes were equal and normal. The diagnosis of ligamentous tear of the extensor musculature was made. Adhesive tape strapping followed by low back support afforded complete relief in 3 weeks. X-ray films (Figs. 3 and 4) revealed transitional type of lumbosacral spine of the 1st sacral segment and large transverse processes of 5th lumbar which articulated with the ilium. The intervertebral space between the 5th lumbar and 1st sacral was narrowed by almost 50 per cent.

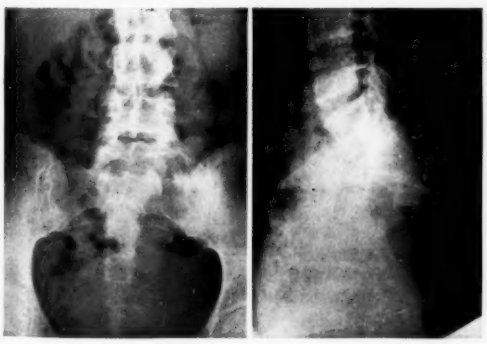
Figs. 1 and 2. Bilateral lumbarization of 1st sacral segment. The benign character of the narrowed interspace is easily appreciated because of the obvious anomalies of the lumbosacral junction.



Figs. 3 and 4. Lateral view reveals narrowing of interspace between 5th lumbar and 1st sacral. Films of this type are misinterpreted, since the transitional character of 5th lumbar is apparent only in the anteroposterior projection.

CASE 3. F. W., negro female, aged 37 years, was referred to the orthopedic dispensary by the gynecological service because of low back pain of 9 months' duration. Nine months previously she had had a hysterectomy for fibroids and she stated that during the convalescence from this operation her low back pain began. There was no history of backache previous to that time and no history of trauma. The pain was rather sharply localized to the midline at the lumbosacral junction and there was no radiation down the legs. Her pain was aggravated by activity, weather changes, and she described her back as being "stiff" in the morning. Examination revealed a markedly obese negress with muscle spasm on both sides at the lumbar level. All back motions were almost complete but guarded. There was tenderness over the spinous processes of the 4th and 5th lumbars. Leg signs were negative, reflexes were equal bilaterally and there were no sensory or motor changes in either leg. Diagnosis was exacerbation of lumbar spondyloarthritis and a long adequate corset was obtained which afforded her almost complete relief. X-ray films (Figs. 5 and 6) revealed a moderately narrowed lumbosacral intervertebral space with the characteristic transitional type of 5th lumbar segment.

CASE 4. F. B., white male, aged 39 years, was first seen in May, 1942, because of low back pain which he ascribed to a fall 17 months previously. At this time he sat down on his buttocks on a cement floor when a wire upon which he was pulling suddenly broke. He had immediate low back pain which had persisted but which was never severe enough to prevent working. There was no history of previous low back pain or back trauma. He complained that his back was sore in the morning and after resting and



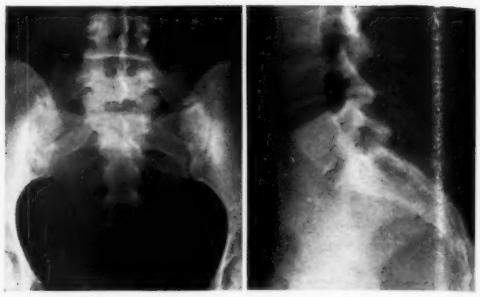
Figs. 5 and 6. The interspace between 5th lumbar and 1st sacral is characteristic of the type midway between the normal thick lumbar and the narrow thin sacral disc. The unilateral lumbarization and incomplete fusion of the lower sacral segments reveal the anomalous character of the 5th lumbar.

Figs. 7 and 8. Fifty per cent narrowing of interspace between the 5th lumbar and 1st sacral. Large lateral elements of the 5th lumbar which do not articulate with the ilium.

Figs. 9 and 10. Type of transitional lumbosacral junction which is less likely to be confusing since the lumbarization of the 1st sacral is so obvious. This was the only case in which an acute lumbosacral angle was noted.

that the pain was aggravated by weather changes. There was radiation of pain down the posterior aspect of the right thigh and lateral aspect of the calf to the level of the ankle. His back pain was worse on lifting. Coughing and sneezing had no effect. There was no paresthesias in the right leg. Examination revealed moderate muscle spasm of both sides of the lumbar level. All back motions were excellent and there was a minimal amount of tenderness over the zygoapophyseal joints over the lower lumbar levels on both sides. Leg signs were normal. Knee, ankle, and Babinski reflexes were negative and there were no motor or sensory changes in either leg. Roentgenograms (Figs. 7 and 8) revealed a healing transverse fracture of the body of the sacrum with arthritic changes of the articular facets at the level between the 5th lumbar and 1st sacral. In addition there was partial sacralization of the 5th lumbar vertebra with the lumbosacral intervertebral disc of the usual intermediate character.

Figs. 13 and 14. Transitional type of 5th lumbar vertebra in a child. The interspace between the 5th lumbar and 1st sacral will persist into maturity in its narrowed character.



Figs. 11 and 12. This type is difficult to evaluate if signs and symptoms suggest herniation of the intervertebral disc. The true character of the 5th lumbar is best appreciated from the anteroposterior view.

Case 5. M. C., negress, aged 52 years, was first seen at the orthopedic dispensary in June, 1942, because of pain in the low back radiating down the posterior aspect of the right leg. In 1936 patient had multiple gonorrheal joints, which were diagnosed by smear and culture, secondary to chronic pelvic inflammatory disease. In October, 1941, she began to develop pain over the right buttock with radiation down the leg. In May, 1942, she experienced recurrence of pain in the shoulder and elbows. She stated that sneezing and coughing aggravated her leg pain as did lying down. The patient had had syphilis many years before for which she had received inadequate therapy. Examination revealed tenderness at the lumbosacral junction in the midline. All back motions were normal. There was about 10 degrees' limitation of straight leg raising on the left. The ankle jerks were equal but the left knee jerk was absent. Babinski was normal and sensory examination was negative. X-ray films of the lumbosacral junction (Figs. 9 and 10) revealed moderately severe spondyloarthritis and spondylitis. In addition there was a lumbarization of the 1st sacral segment with an acute lumbosacral angle. The diagnosis was traumatic arthritis secondary to an asymmetrical, mechanically poor lumbosacral junction on a congenital basis.

Case 6. A. J., negro female, aged 22 years, was seen in the orthopedic out-patient dispensary in May, 1942, when she complained of sudden onset of low back pain of 6 weeks' duration. There was no history of trauma and her low back pain was constant with radiation down the lateral aspect of both thighs as far as the knee. Stooping was impossible because of pain. Examination revealed exaggeration of the normal lumbar lordosis with considerable limitation of all low back movements due to muscle spasm. There was tenderness at the lumbosacral level at the midline. Straight leg raising was possible to 90 degrees on both sides. Neurological examination was negative. The impression was low back strain aggravated by obesity. X-ray films (Figs. 11 and 12) revealed lumbarization of the 1st sacral

segment with large transverse processes of 5th lumbar which articulated with the ilium. The patient was placed in a low plaster jacket which has afforded her complete relief.

In these 6 cases, the pain can be adequately explained on a basis other than herniation of the intervertebral disc. The absence of leg signs or reflex changes plus their excellent response to conservative management bespeak against a disc pathological process.

With the recent emphasis that has been placed upon the making of the diagnosis of the herniated intervertebral disc without the use of lipiodol or other contrast media, it would be reasonable to believe that the presence of a narrowed intervertebral space in doubtful cases might give the operator a false sense of security.

While it has been generally recognized that narrowing of the intervertebral space does not necessarily imply a pathological process, it still is not generally understood that a diminution in the height of the intervertebral space in the presence of anomalies may exist without clinical significance. X-ray pictures which fail to reveal lipping or sclerosis of the vertebral bodies or zygoapophyseal joints localized to the level of the lumbosacral junction but whose lumbosacral intervertebral disc has been reduced, still are being interpreted as evidence of herniation of the disc. While it is admitted that many cases whose x-rays reveal no stigma of trauma except narrowing are instances of protruded discs, still more careful observation for congenital anomalies is demanded before such an opinion can be unequivocally expressed. The routine interpretation of narrowed intervertebral space on such x-ray films as the expression of a ruptured intervertebral disc obviously is absurd, yet such an opinion is still all too frequently encountered.

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A COMPARISON OF THE EFFECTS OF TANNING AGENTS AND OF VASELINE GAUZE ON FRESH WOUNDS OF MAN

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CERTAIN criticisms have recently been made of the tannic acid method of treating burns. Although the use of tannic acid for the treatment of burns has been widely adopted, some surgeons have found that burns covered with vaseline-impregnated gauze heal more rapidly than comparable burns treated with tannic acid. Since there are numerous conflicting opinions regarding the efficacy of various types of burn therapy, we decided to compare the tissue alterations due to tanning agents with the tissue alterations found following the application of vaseline gauze.

Davidson introduced the tannic acid method of burn treatment in 1925, because of his belief that burned tissue liberated substances responsible for the so called "burn toxemia." Since "tannic acid forms a more or less stable compound with the protein constituents of body fluids and cells," he hoped that it would precipitate "the poisonous materials in burned tissue and thereby prevent their absorption." Davidson was aware that tannic acid, especially in high concentration, might have a possible deep caustic action, and therefore he advocated that it be applied as a 2½ per cent solution in the form of wet compresses. Furthermore, the burns were to be inspected at 12, 18, and 24 hours for evidence of tanning, and as soon as the surface assumed a light brown color, the application of tannic acid was to be discontinued.

There have been many modifications in the method of applying tannic acid. Perhaps the most important of these is that of Bettman in which a single application of 5 per cent tannic acid is followed by a single application of 10 per cent silver nitrate. Bettman claims that this method is superior to tannic acid alone because it produces a thin, flexible eschar—and this almost instantaneously instead of over a period of 12 to 24 hours. The introduction of tannic acid revolutionized the treatment of burns, and today probably more burns are treated with tannic acid alone or in combination with silver nitrate than with any other method.

In spite of the wide use of tannic acid there have been comparatively few anatomic studies of the effects of tanning agents on damaged or normal tissues. Loehr and Zacher, in 1933, reported their observations on the comparative effects of cod liver oil ointment and of tannic acid applied to burns on domestic pigs. They selected the pig, as they believed its skin to be the most suitable for the production of experimental burns. Deep ulcers extending to the subcutis and muscularis were produced by the application of hot soldering irons for ten seconds. Tannic acid or cod liver oil ointment was then applied to the burned areas. The experimenters found that the burns treated with cod liver oil healed more quickly than did those treated with tannic acid. From examination of biopsy specimens of the burned areas obtained at 3 and 6 days, they concluded that the tissues of burns treated by tannic acid appeared to be torporific so that healing was delayed. They noted that an eschar formed when the tannic acid came into contact with the dermis but failed to form when applied to fatty tissues. The histological findings were too incompletely recorded to enable one to judge in detail the reactions of the tissues to the medicants applied.

Taylor, in 1936, called attention to the destructive effects of tannic acid which he observed in biopsy specimens taken from rabbits following the application of tannic acid to

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their skins. Since the cornified layer of the rabbit's epithelium is thin and is of little protective value against tannic acid, the tannic solution penetrated deeply to destroy the entire epithelium. Taylor also studied a biopsy tissue from a human burn which had been treated by tannic acid. His observations led him to suggest that tannic acid may damage normal structures.

Anagnostidis has made the most complete study of tissue reactions to medicants applied for the treatment of burns. He produced burns on rabbits by hot water and hot irons with destruction of the epithelium and a portion of the corium. Various medicants were applied to the burns, including tannic acid solution, tannic acid plus silver nitrate, bismuth dressings, and cod liver oil ointment. Some of the experimental burns were completely excised after 48 hours, others at 10 days, and the prepared sections were stained by appropriate methods. From examination of the biopsy specimens Anagnostidis found the medicants deposited in irregular clumps on the surface and portions within the eschar. He also found that some of the materials had penetrated the epithelial cells and the corium. In the biopsy specimens taken at 10 days the necrotic layer had separated from the viable remaining dermis which had become completely re-epithelized from the edge of the burns. Anagnostidis presented the startling conclusion that all the experimental burns healed with equal rapidity regardless of the treatment applied. Furthermore, he was unable to find any histological differences in the treated and the untreated lesions.

In some of the studies mentioned it has been suggested that the coagulating action of tannic acid produces damage to normal structures. If this hypothesis be correct, tanning agents applied to superficial burns may produce further damage by destroying the basal layer of the epithelium and the glands of the corium which serve as sources of regenerating epithelium. It would seem important to know the effects of various medicants on normal tissues if these materials are to be applied to tissues damaged by burns. Since a thorough knowledge of the effect of tanning agents and of vaseline gauze on normal and burned tissues is not available, we decided to investigate the problem.

Fig. 1. Control. Biopsy specimen from donor site immediately after removal of graft with dermatome. ×85.

MATERIALS AND METHODS

The ideal way to study the effect of tannic acid on the tissues beneath burned epithelium would be to take biopsy specimens of the burn before the application of tannic acid and at suitable intervals after. There are, however, certain difficulties in applying such a procedure to humans. Furthermore, accidental burns are not of uniform depth, and one has no guarantee that several specimens removed from a burn will be from areas of equal tissue destruction. This is true even though the specimens be taken within a half inch of each other. In order to determine how much of the destruction is due to tannic acid, it is necessary to begin with a burn of constant depth. It is not possible with humans to obtain an accidental burn of constant depth, but it is possible to obtain a skin injury of constant depth through use of the Padgett dermatome. This machine, originally developed by Padgett for the purpose of cutting Thiersch and split thickness grafts, enables one to remove a uniform layer of skin of almost any desired thickness. When a layer of skin is removed by means of a dermatome, the knife usually removes the epithelium completely plus a narrow portion of the papillary layer of the corium. The hair follicles, the sweat glands, and the sebaceous glands in the remaining corium are left unharmed (Fig. 1). These structures will serve as the source of

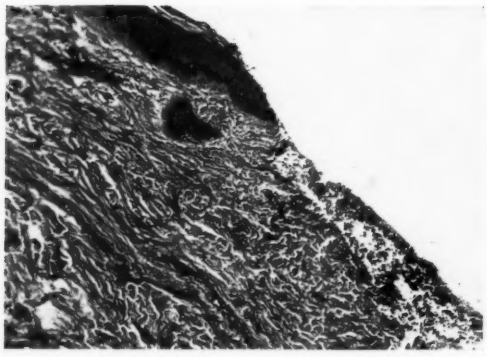

Fig. 2. Vaseline gauze treated donor site at 1½ hours. ×85.

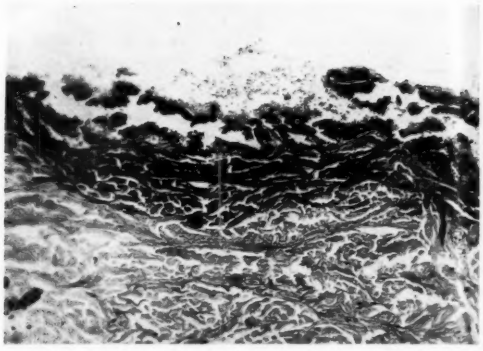

Fig. 3. Tannic acid treated donor site at 1½ hours. ×85.

cells which will re-epithelize the surface of the naked dermis. The lesion produced, except for the presence of a layer of burned epidermis, simulates a second degree burn. If tannic acid or similar materials are capable of destroying normal tissues, their action should be manifest upon their application to such a surface.

A number of opportunities were afforded us to apply tannic acid to such surfaces in patients who were to receive skin grafts. Under spinal or general anesthesia, the skin was washed thoroughly with soap and water. It was then cleansed with 70 per cent alcohol, followed by ether, in order to provide a dry surface. The cement which is used in conjunction with the Padgett dermatome was applied, and after it had dried, grafts were cut approximately 0.016 inches in thickness. Bleeding was controlled by pressure with gauze moistened with warm physiological saline solution. As soon as the bleeding was controlled, the donor site was sprayed with a freshly prepared solution of 10 per cent tannic acid (pH 3.4). After a few minutes this was followed by a spray of 5 per cent silver nitrate. On the same patient a similar area was prepared as a control. It was covered by a fine mesh gauze impregnated with vaseline. At intervals biopsy specimens for microscopic study were removed under local procaine anesthesia from both donor sites. The specimens obtained were placed in 10 per cent formalin, embedded in paraffin, and stained with hematoxylin and eosin.

A few patients were treated with a burn jelly containing quebracho tannin 7.5 per cent and meta-di-hydroxy-di-secondary-hexylbenzene, 1:1000, in a water soluble base. This preparation was used as quebracho tannin has been proposed as a substitute for tannic acid.

The number of times that one can persuade a patient to subject himself to removal of a piece of skin for microscopic examination is limited. However, specimens were obtained from a total of 12 patients at irregular intervals up to 10 days, and a complete series of specimens from 1 to 150 hours was obtained from 2 patients. The histological observations recorded here and the photomicrographs presented represent a compilation of all the biopsies studied. Since tannic acid plus silver nitrate and quebracho were found to produce similar tissue changes, the tanning agent used on a specific donor site will not always be specified in the histological observations.

Observations on patients. The donor sites which were treated with vaseline gauze without exception healed more rapidly than those treated with the eschar-forming substances. In 10 to 14 days re-epithelization was complete in the wounds treated by vaseline gauze while the sites treated with tannic acid and silver nitrate or quebracho burn jelly required from 14 to 21 days for re-epithelization. The patients complained that donor sites treated with tannic acid were more painful than similar sites treated by vaseline gauze, and many asked that vaseline gauze alone be used at subsequent graftings.

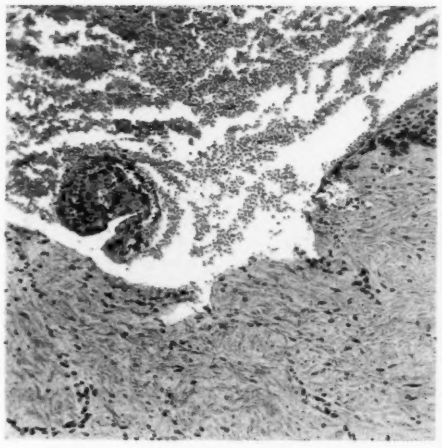

Fig. 4.

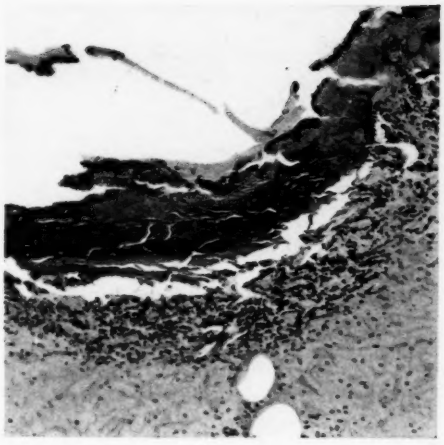

Fig. 5.

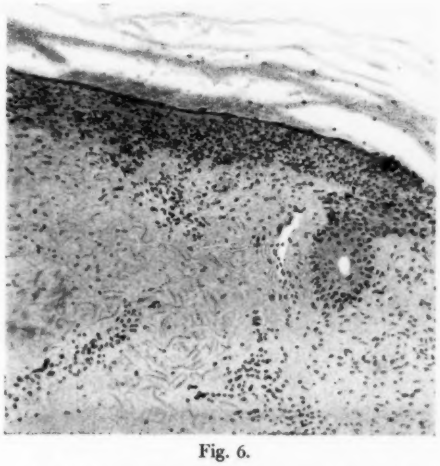

Fig. 6.

Fig. 7.

Fig. 4. Vaseline gauze treated donor site at 8 hours. ×100.

Fig. 5. Tannic acid treated donor site at 8 hours. ×100. Note thickness of eschar and leucocytic exudate.

Fig. 6. Vaseline gauze treated donor site at 24 hours. ×100.

Fig. 7. Tannic acid treated donor site at 24 hours. Note extensive coagulation of dermal collagenous bundles. ×100.

A Comparison of the Effects of Tanning Agents and of Vaseline Gauze on Fresh Wounds of Man. —*John Winslow Hirshfeld, Matthew A. Pilling, and Mark E. Maun.*

Histological observations. At 2 hours wounds treated with vaseline gauze showed a mild exudate of fibrin and red blood corpuscles on the dermal surface with no destruction of collagenous bundles, and as yet no exudate of leucocytes in the area (Fig. 2). Biopsy specimens taken from those wounds treated by tannic acid and silver nitrate showed a thick layer of brownish-black material covering the exposed dermis. A marked exudate of red blood corpuscles and large clumps of fibrin were found beneath the tanning agents (Fig. 3).

Several specimens were available to compare the effects of tannic acid and of vaseline gauze at 8 to 10 hours following their application. Donor sites treated with vaseline showed a mild red blood corpuscular and fibrinous exudate with a moderate number of leucocytes in the superficial portions of the dermis and upon its free surface. This leucocytic exudate consisted of about equal numbers of neutrophils and mononuclears, the latter being lymphocytes and plasma cells. The superficial collagenous bundles showed no abnormalities (Fig. 4). Examination of comparable sections treated with tannic acid and silver nitrate revealed the superficial dermal bundles to consist of an acidophilic homogeneous mass covered by the tanning mixture. Beneath the eschar granules of the tannic acid could be found at a surprising depth between other collagenous fibers. The tannic granules produced considerable variation in the staining qualities of the collagenous fibers, and the edges of some of the bundles stained a deep blue; these changes undoubtedly represent early tissue damage (Fig. 5). The more superficial tannic-impregnated homogeneous mass was interrupted by many crevices which widened to produce a separation from the deeper viable dermis. In the latter an intense leucocytic exudate was found.

Biopsy specimens were taken from only 1 patient 24 hours following treatment of the donor sites. Examination of the specimen taken from the wound treated by vaseline gauze showed numerous leucocytes on the surface of the dermis. These cells had apparently invaded viable normal staining collagenous tissue. A necrotic layer could be detected upon the most superficial portion of the dermis. Inspection of the sweat glands and the hair follicles showed some proliferation of their epithelial cells; this proliferation likely represents an early attempt at epithelization (Fig. 6). The donor site treated by tannic acid showed an extensive coagulation of the dermal collagenous bundles; the destruction of the dermis extended many times deeper than the inflammatory exudate seen in the vaseline treated donor site. The separating eschar carried with it numerous necrotized sweat glands which would have served as epithelial islands in the repair process (Fig. 7).

A number of biopsy specimens were available for examination in the period from 30 to 60 hours following therapy. Donor sites treated with vaseline gauze showed an increased inflammatory exudate in and upon the dermis. The exudate was chiefly neutrophils embedded in small amounts of fibrin. In a few areas there was some destruction of the superficial portions of the dermis due to this exudation. Small patches of proliferating epithelial cells could be found spreading through the exudate partially to cover the collagenous fibers. Tissue sections showing the effect of tannic acid therapy revealed continued destruction of large portions of the dermis. In addition, an extensive leucocytic exudate was seen at the base of the separating crust. The process extended in some instances almost to the subcutis. Small areas of epithelial regeneration could be seen in some sections.

Specimens taken from 4 patients at 60 to 80 hours following the application of vaseline gauze and of tannic acid were available for study. In those patients treated by vaseline gauze a layer of leucocytes and fibrin was seen on and in the superficial portions of the dermis. Most of the leucocytes were neutrophils, but a few lymphocytes and monocytes could be seen. Unquestionably there were some damage and destruction of the dermal collagenous fibers due to the infection present, but it was superficial in character. In the sections which were obtained 70 hours following therapy, definite epithelial masses could be found spreading over the corium; in some

instances the epithelial cells appeared to be penetrating the leucocytic exudate.

Examination of sections treated with tannic acid showed the wounds to present a layered effect. The superficial portion was stained a deep blackish-brown because of a heavy precipitate of the tanning material. Collagenous fibers immediately beneath the superficial layer appeared as a glistening homogeneous mass staining lightly with eosin. The deepest layers were made up of strands of collagenous fibers taking an intense eosin stain. A few of these were smooth and homogeneous, and the entire layer was extensively infiltrated with leucocytes. This deep layer was thicker than the entire layer of damaged tissues in the vaseline treated wounds and contained an equal leucocytic exudate. In some sections all layers of the damaged dermis had separated from the underlying viable collagenous fibers while in others the superficial and middle layers were breaking away. These observations indicate that destruction of tissue is deeper than the firm eschar found covering the wound. Arm-like epithelial masses were spreading beneath the deep leucocyte invaded layer. Immediately beneath the newly formed epithelium focal collections of neutrophils and lymphocytes were found, and the surrounding dermal fibers stained normally with eosin. No granules of tannic acid were present.

Biopsy specimens from 2 patients were taken between 80 and 150 hours following application of vaseline gauze or tannic acid. During this period the leucocytic exudate in the vaseline gauze treated wounds was less marked than in the previous sections, and almost complete epithelization was seen. Beneath the newly formed epithelial cells a small amount of exudate was present; it consisted of focal collections of lymphocytes and plasma cells. Small masses of neutrophils could also be seen upon the epithelium. Sections from the wounds treated by tannic acid showed changes like those in the biopsies taken about 80 hours after therapy. Epithelization was almost complete. The leucocytic exudate beneath the epithelium had subsided, and the superficial dermal fibers were lightly stained.

Biopsy specimens from 2 patients were obtained 5 to 10 days following the creation of the wounds. In those treated by vaseline gauze epithelization was complete. Collagenous fibers beneath the epithelium stained less intensely than did the more mature deeper bundles, and a few lymphocytes were found among these light staining fibers. Sections taken from the tannic acid treated areas showed thick leucocytic exudates over the newly formed epithelial bridges. Beneath the epithelium focal collections of lymphocytes were present. At 5 days epithelial regeneration was complete, but the epithelium was still quite thin.

SUMMARY

Many surgeons have suspected that tannic acid may have a destructive effect on tissues; therefore they have advocated the use of non-irritating medicants for the treatment of burns. A review of the literature reveals little anatomic evidence to confirm or disprove the forementioned concept. A few experimental studies suggest that tannic acid probably injures normal tissues, but the evidence is not conclusive. We had an opportunity to compare the reaction of normal tissues to tannic acid and to vaseline impregnated gauze by applying them to donor sites of individuals who were receiving skin grafts.

Patients complained that the stiff eschars on donor sites treated with tannic acid caused considerable pain while comparable donor sites treated with vaseline gauze were relatively painless. On inspection it was found that the donor sites treated by vaseline gauze healed more quickly than those treated by tannic acid. Biopsy specimens of the treated donor sites were taken whenever the patients would submit to the procedure. A sufficient number of specimens were obtained to permit a study of tissue reactions to the medicants during a period ranging from several hours to 10 days. From study of these specimens we found that, to form the eschar, the tanning agents destroyed the dermis to a great depth. In addition, a marked leucocytic exudate was found beneath the eschar with further destruction of the collagenous bundles of the dermis. The portions of the epithelial structures contained in these layers were destroyed so that epithelization finally took place beneath the exudate. Vaseline gauze proved to

be nonirritating to the exposed dermis; hence only a mild red blood corpuscle and leucocytic exudate was found. The only visible damage to the dermis was in those cases showing some infection. Re-epithelization from the uninjured dermal glands was more prompt in the donor sites treated by tanning agents.

CONCLUSIONS

1. Donor sites heal more quickly with less discomfort when treated by vaseline gauze than when treated by tannic acid.

2. Tanning agents produce extensive tissue damage to the dermis to form the eschar while vaseline gauze produces a minimal damage.

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STRUMA LYMPHOMATOSA

Hashimoto's Disease

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THROUGHOUT the literature on diseases of the thyroid there exists a controversy as to the relationship of the entity first described by Riedel (29) called "*Eisenharte Struma*" to that first described by Hashimoto called "*Struma Lymphomatosa*." On the basis of a study of the literature and our own cases we have concluded that there is no relationship between the 2 diseases and will attempt to bring out data to support this contention.

HISTORICAL REVIEW

Riedel (29, 30) in his original papers reported 5 cases of which 3 were males and 2 females. The striking clinical manifestation in all of the cases was the hardness of the tumor which suggested a malignant lesion. At operation this finding was confirmed and the thyroid was found to be attached to the trachea, the carotid artery, and the internal jugular vein. Upon microscopic examination Riedel stated that he observed both spindle and round cells but when his drawings are inspected one is impressed by the dense infiltration of connective tissue. Lymphoid cells are present in only small numbers and lymph follicles are absent.

Hashimoto reported 4 cases, all of which were females. The tumors were firm but not hard. At operation there was fixation to the trachea but not to other tissues. Although there was rich infiltration with connective tissue, the change he emphasized repeatedly was the presence of lymphocytes, diffuse and in the form of lymphoid follicles of varying size with germinal centers.

Ewing studied 4 cases and stated that "in two of them very extensive and peculiar sclerosis had overtaken and largely replaced the lymphoid tissue." He concluded that "Hashimoto and Riedel have described the early and late stages of the same pathological process . . . Fibrosis and hyaline transformation begin early and eventually, as in Riedel's disease, the enlarged gland becomes firm and dense."

Foot, in a personal communication to Poer took the opposite view. He stated that "Hashimoto's struma has no connection with Riedel's struma and they represent two distinct processes—the one an overgrowth of lymphoid tissue, followed later by fibrous invasion that may be more a metabolic than an inflammatory process—the other a fibrous overgrowth in response to some inflammatory stimulus. In Hashimoto's disease we have the lymphoid tissue growing as lymph follicles among the parenchymatous portion of the gland and crowding it out in that way, but without the enormous fibrous reaction of Riedel's struma. In the latter the fibrous overgrowth seems to strangle the parenchyma slowly but certainly, until it undergoes almost total atrophy and is replaced by dense woody masses of connective tissue. The lymphatic invasion in that case consists more of lymphocytes than of lymphoid tissue with germinal centers as is seen in Hashimoto's disease."

Joll (13) pointed out the confusion that exists in the literature in the interpretation of these two lesions. He described 51 cases of his own and 30 communicated to him. He emphasized in Riedel's struma the absence of diffuse lymphocytic infiltration and of lymphocytes, although admitting the presence of an occasional lymph follicle. He considered Hashimoto's disease a separate entity both clinically and pathologically from Riedel's struma.

Graham (6) thought that Riedel's struma was not always preceded by Hashimoto's disease and that Hashimoto's disease did not necessarily progress to Riedel's, and thought it improbable that there was any essential rela-

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tionship between the two. He stated that both clinical and microscopic findings were necessary to differentiate them and suggested that clinicians record the following data on their cases: age, sex, previous goiter; duration of symptoms; duration of goiter; extent and character of involvement of the thyroid; limitation of the process to the thyroid or extension beyond it (including more than a mere statement that the gland was adherent); adhesions to trachea as opposed to adhesions to surrounding structures; presence in the thyroid of adenomas, cysts, areas of calcification, frank inflammation, including small or large abscesses; presence or absence of hyperthyroidism or hypothyroidism before and after operation; amount of tissue removed; character of thyroid remaining and gross and microscopic findings.

Lee considered struma lymphomatosa and Riedel's struma separate entities. In his review of the literature in 1935 he accepted 26 cases as Hashimoto's and 90 as Riedel's disease. Only 1 case of struma lymphomatosa occurred in a male.

The only experimental work directly related to struma lymphomatosa which was found was done by McCarrison. He fed to rats a diet of American white flour, 72 to 80 parts; meat residue, 5 to 15 parts; olive oil, 8 parts; salt mixture containing 0.45 per cent potassium iodide, 5 parts; and distilled water, *ad lib.* Various modifications of this with greater or less amounts of white flour or with certain proportions of white flour replaced by starch were also used. Twenty-five per cent of the young rats fed on such diets had goiters of various sizes at autopsy. The goiters were found as early as 75 days and as late as 165 days after beginning the experiment and occurred more frequently in the female. Grossly the glands were glistening, fleshy, bright red or dark red, and 2.5 times normal size. The isthmus was usually prominent, thickened, and hardened. In the majority of instances the enlargement was bilateral with one lobe larger than the other but occasionally the enlargement was unilateral. His photomicrographs showed interacinar infiltration with lymphocytes with a follicle without a germinal center. He suggested that the occurrence of the disease in humans might be due to ingestion exclusively of white flour or other vitamin-poor carbohydrates, vitamin-poor protein, vitamin-poor fats, and a scarcity of fresh fruits and green vegetables.

Boyden, Coller, and Bugher stated that "when one is afforded the opportunity to study pathological specimens from a series of cases, it is immediately apparent that different degrees of lymphocytic infiltration and lymph follicle formation as well as varying grades of fibrosis occur, not only in different glands but also in various portions of the same specimen. With this in mind, it becomes impossible to segregate them (Hashimoto's and Riedel's disease) into two distinct pathological entities." In discussing McCarrison's work they said "McCarrison considered this to be the result of dietary deficiency but it is equally good evidence of the possible rôle of iodine in the production of this type of thyroid disease."

Lee and McGrath (17), indirectly quoting Joll (14) and Graham and McCullagh (7) stated:

> "1. Hashimoto's struma is confined almost entirely to women over the age of 45 years while Riedel's disease usually occurs in adults but may appear at any age, and men are affected nearly as often as women.
>
> "2. Regardless of operative treatment, patients with lymphadenoid goiter tend to develop myxedema, frequently preoperatively. Riedel's disease, even after extensive resection, rarely leads to defective function.
>
> "3. Lymphadenoid goiter is diffuse from the outset and no part of the gland escapes. Localization to a lobe or part of a lobe is common in Riedel's struma.
>
> "4. Widespread formation of delicate connective tissue is characteristic of the late stages of lymphadenoid goiter, while dense fibrosis comparable to scar tissue or keloid formation is found even in the earlier stages of Riedel's disease."

COLLECTED CASES

In a review of the literature it is difficult, from evidence reported, to select the true instances of Hashimoto's disease. This difficulty is due partly to the absence of an arbitrary standard, the diagnosis being a matter of opinion of the individual author, and partly to insufficient data in the report. In a complete review of the literature we found only 71 cases which were reported in sufficient detail to accept as unquestionable Hashimoto's disease. A few of the cases reported were not included because of incomplete data. Some cases which we considered true instances of struma lymphomatosa were originally reported

under another diagnosis, most commonly that of Riedel's struma.

Incidence. Lee (18), at Presbyterian Hospital in New York, found 3 cases in 1,800 thyroidectomies; Joll (13), 51 cases in 5,650 thyroidectomies; while G. Keynes in a personal communication to Joll recorded 25 cases in 1,600 patients in whom the thyroid had been removed. At the New York Hospital over a period of 10 years from 1932 to 1942 in 1,999 thyroidectomies there were 15 cases of Hashimoto's disease. Thus in 11,049 operations on the thyroid the incidence was one in 116 or slightly less than 1 per cent.

A summary of the data on the 71 cases of Hashimoto's disease is presented as follows:

The age in these cases varied between 14 and 75 years, the average being 47 years; the majority of patients, 39, presented themselves for treatment at 41 to 60 years of age. There were 2 patients in the 2d decade of life; 7 in the 3d; 12 in the 4th, 19 in the 5th; 20 in the 6th; 7 in the 7th; 4 in the 8th. There were 68 females and 3 males (10, 16).

Clinical manifestations. In most of these patients a goiter or swelling in the neck was the chief complaint. The duration of symptoms was from 5 days to 32 years, most commonly, however, from 1 month to 5 years. Loss of weight was more common than the gain which one might expect. Of those in which it was recorded, 11 patients lost, 4 remained constant, and 3 gained weight. The presence or absence of nervousness was mentioned in 21 patients of whom 13 complained that they were nervous while 8 said they were not nervous. The lesion grew slowly in 28 cases, rapidly in only 3, and in 1 the rate of growth was slow until the 3 months before admission to the hospital and then rapid. Pressure symptoms noted were hoarseness, dysphagia, aphonia, tight feeling in the throat, pressure in the neck, stridor or substernal pressure, pulling sensation in the neck, coughing, and change in voice. In 48 cases one of the above pressure symptoms was present while in only 2 is it noted that they were all absent. Other symptoms listed were loss of sleep, anorexia, palpitation, pain in neck, hypertension, fatigability, menorrhagia, metrorrhagia, vertigo, headache, weakness, increased appetite, indigestion, nausea and vomiting, swelling of ankles and hands, tachycardia, mental depression, fainting, tremor, and hot flashes.

As regards the state of nutrition of these patients it is recorded that 22 were well developed and well nourished and 4 obese; while in 1 patient malnutrition was noted. The blood pressures were given in 33 patients; in 6 it was over 200, in 10 between 150 and 200, while in 16 it was 100 to 150. Only 1 instance of a blood pressure below 100 was found.

General statements in regard to the size of the gland indicate that the enlargement was slight in 16, moderate in 31, and marked in 9 cases. In the 71 collected cases 46 were described as showing uniform enlargement, involving both lobes and the isthmus; in 6 only 1 lobe and the isthmus were affected while in 3 a single lobe was enlarged. In 16 this feature is not mentioned. The presence or absence of fixation was not mentioned in 43 cases; in 16 it was stated that the thyroid was not fixed. Of the remaining cases 12 were described as fixed; in 3 the attachment being to the trachea, in 3 to other tissues including muscle or large vessels and in 6 the point of fixation was not given. Fixation is not a common feature.

The preoperative basal metabolic rate ranged from plus 63 to minus 23, tending on the whole to be slightly elevated. The average of the 41 recorded cases was plus 5. Postoperative tests on 20 patients at intervals ranging from 2 months to 8 years after operation were found to vary from plus 3 to minus 45 and to average minus 4. The average fall after operation was 19 points in the recorded cases.

Operative findings. The operative findings in regard to the presence or absence of uniformity of enlargement coincided with the clinical findings. Forty-four cases showed bilateral involvement with uniform changes; in 6 the isthmus alone, one lobe or one lobe and the isthmus were enlarged. No data were given on the others. The presence or absence of adherence is mentioned in 39 cases. Absence of adhesions was noted in 17; 23 were described as being attached to the trachea of which 10 were also adherent to muscles, large vessels, and surrounding tissues. Vascularity was mentioned in 17 instances, being described as slight in 13 and marked in 4.

Pathology. Gross: The weight of the gland varied from 17 to 340 grams, the average being 91 grams. The gland was described as firm in 27 cases, hard in 20, and soft in 2.

Microscopic: The thyroid acini tended to be small and atrophic with only a few showing areas of hyperplasia. In 38 cases the acini were atrophic, in 7 hyperplastic, in 4 normal, and in 4 atrophic with areas of hyperplasia. The acinar cells were usually small and low cuboidal with central nucleoli and were only rarely columnar. Colloid, in the main, was scant and in 24 cases was described as rare or little, in only 6 as normal, and in 7 it was noted that no colloid was present. Lymphoid elements were present in all cases, no case having been included unless it was stated that lymphoid elements were present or unless they could be seen in the photomicrograph. In 66 cases there was diffuse lymphoid infiltration and in 64 lymphoid follicles were present; in only 2 was a statement made that lymph follicles were not present. Germinal centers were described in only 7 cases although in none of the others was the statement made that such centers were absent. On the whole this lymphoid tissue was widespread and abundant. In 47 cases the amount of connective tissue was noted; in 17 of these it was scant or slight, in 20 moderate, and in 10 marked.

Follow-up. Follow-up reports in the cases cited in the literature are unsatisfactory. Few late results were given and the metabolic rate, when noted at all after operation, was usually recorded only up to 6 months after thyroidectomy. Only 3 patients had basal metabolic tests as late as 2 years after operation.

NEW YORK HOSPITAL CASES

Table I gives a summary of the 15 cases of struma lymphomatosa treated at the New York Hospital.

Clinical manifestations. The youngest patient in this group was 26 years of age, the oldest 60, and the average age 43.6 years. All patients in this group were women. In 13 patients the chief complaint was goiter, in 1 nervousness, and in 1 dyspnea and fatigability. The duration of symptoms varied from 9 months to 25 years, the average being 5 years. Weakness or fatigue was noted in 5 patients,

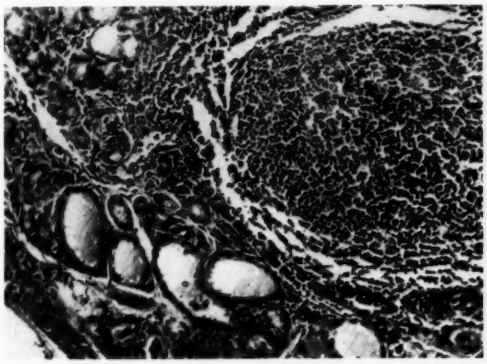

Fig. 1. Photomicrograph showing thyroid acini with cuboidal epithelium containing small amounts of thin, poorly stained vacuolated colloid. A lymphoid follicle with a well formed germinal center is present and connective tissue is scant. × 215.

weight loss in 3, and weight gain in 1; nervousness in 8; fever in none; slow growth of the goiter in 14; pressure symptoms such as hoarseness, dysphagia, or choking were noted in 6 patients and dyspnea on exertion in 7.

Physical examination: Objectively fever was not found to be present in any patient. The pulse rate varied from 68 to 115 and averaged 93.6 per minute. The lowest blood pressure was 96/50 and the highest 204/100, the remainder of the readings being within normal limits. Seven patients were described as well developed and nourished, 1 as slightly obese, 4 as obese, and 1 as malnourished, while in 2 the state of nutrition was not stated. The gland usually was described as slightly to moderately enlarged; only 1 was said to be tremendously enlarged. All were referred to as nodular save 1 in which the presence of nodularity was not mentioned. In no case was fixation noted. Roentgenograms of the chest and neck taken before operation showed nothing abnormal except a soft tissue mass in the neck of 7 patients, a mass extending slightly into the thorax in 1 and tracheal deviation and compression in 1 case.

Laboratory findings. The lowest blood count was 4,300, the highest 12,300. In 10 cases a differential count is recorded; the lymphocytes ranged between 23 and 47 per cent with an average of 36 per cent. There was no variation from normal of the other blood cells.

TABLE I.—NEW YORK HOSPITAL CASES

Case Hospital Number Age	History	Duration Years	Weight Kilograms	Pulse	Blood pressure	B. M. R.—before and after operation	Gross Pathology			Microscopic Pathology			Follow up	
							Size Grams	Uniformity	Consistency	Acini	Lymphoid infiltration	Stroma		
1. RC 30343 38	Hoarseness	2½	72.5	92	120/80	Slightly minus before	40	Not uniform Nodular	Cystic Areas of calcification	Medium little colloid	Diffuse, complete Large follicles Germinal centers	Scant	36 mos. B.M.R. —25	Hypothyroidism Thyroid No goiter
2. EM 97329 60	Goiter Fatigue	Several	59.1	70				Uniform	Muscle-like	Atrophic	Interacinar Small follicles Germinal centers	Scant		
3. EC 97828 26	Goiter Fatigue	1	47 (11 lb. loss 1 yr.)	112	148/80	+26 before —5 6 mos. after	39	Not uniform	Stony hard nodular	Small, with colloid	Interacinar Numerous follicles Germinal centers	Scant	66 mos. Wt. 61.3 kg. B.M.R. +16	Hyperthyroidism No goiter
4. EA 105678 48	Goiter Nervousness Palpitation	¾	46 (10 lb. loss 9 mo.)	115	138/86	+16 before —4 2 wks. after	13	Not uniform	Pearly white	Small, moderate colloid	Interacinar Many follicles Germinal centers	Scant	78 mos. Wt. 58.7 kg. B.M.R. —2	Hypothyroidism No goiter Thyroid ‡
5. TA 133335 54	Goiter		58.4	90	120/70		42	Uniform	Soft flabby	Atrophic, medium colloid	Scattered follicles Germinal centers	Scant	66 mos. Wt. 60.6 kg. B.M.R. —5	Hypothyroidism No goiter Anemia Thyroid ‡
6. RE 148254 47	Goiter Nervousness	Many	58	76	116/70	None before Plus minus 0 2 wks. after	42.5	Nodule in isthmus	Firm Granular Extra pale	Small, little colloid	Uniform Small follicles Germinal centers	Scant	42 mos. Wt. 56.5 kg. B.M.R. +8	Hypothyroidism No goiter Thyroid ‡
7. MK 196749 39	Nervousness Palpitation Exophthalmos	10	60.5	100	112/72	—15 before —16 2 wks. after	55	Homogenous	Resembling youthful fat	Few small, little colloid	Diffuse, complete Small follicles Germinal centers	Scant		
8. RC 231057 26	Nervousness Dyspnea Hoarseness	2	47.3	112	120/56	+5 2 wks. after	20	Uniform	Flabby	Small, little colloid	Diffuse, complete Small follicles Germinal centers	Scant	30 mos. Wt. 48.1 kg. B.M.R. —12	No hypothyroidism No goiter Normal
9. OL 233143½ 46	Goiter Dyspnea	10	74.6	86	150/80		165	Not uniform	Soft	Small, medium colloid	Scattered follicles Germinal centers	Fairly diffuse	6 mos. No increase General condition excellent	No hypothyroidism No goiter
10. HP 260076 39	Goiter Fatigue Dysphagia	4	76.8 (60 lbs. loss 6 yr.)	100	122/78	—2 before	122	Uniform	Smooth	Small, medium colloid	Uniform Many follicles Germinal centers	Scant	24 mos. Wt. 74.8 kg. B.M.R. —4	Hypothyroidism No goiter Thyroid ‡
11. MJ 265954 53	Goiter Dysphagia Dyspnea	25	73.2	98	96/50	—2 before	177	Fairly uniform	Very hard	Small, little colloid	Uniform Numerous follicles Germinal centers	Fairly profuse	18 mos. Wt. 81.6 kg. B.M.R. —19	Hypothyroidism No goiter Thyroid ‡
12. MN 273129 54	Goiter Hoarseness Choking	4	82 (Gained 40 lb. 4 yr.)	94	204/100	—6 before Plus minus 0 1 wk. after	58	Nodular		Small, little colloid	Uniform Few follicles No definite centers	Extremely scant	24 mos. Wt. 74 kg. B.M.R. —11	Hypothyroidism No goiter Thyroid ‡
13. ML 276601 45	Goiter Dyspnea	¾	87.2	96	120/80	—5 before	93	Uniform	Very firm pale	Small	Not uniform Numerous follicles Germinal centers	Fairly profuse	18 mos. Wt. 89 kg. B.M.R. —1	Hypothyroidism No goiter Thyroid ‡
14. VB 233756 49	Goiter	5/6	61.7	68	130/82	Normal before —13 3 mos. after	54	Uniform	Firm	Medium little colloid	Diffuse, complete Numerous follicles Germinal centers	Moderate	2 mos. B.M.R. —13	Hypothyroidism No goiter Thyroid ‡
15. AR 265893* 32	Dyspnea Fatigue	2	40	96	130/86	+4 before —15 2 wks. after	7		Firm	Small, little colloid	Diffuse, complete Numerous follicles Germinal centers	Moderate	7 mos. B.M.R.—15	Hypothyroidism Left lobe palpable Anemia Thyroid ‡

*All patients were women and all were subjected to subtotal thyroidectomy, except the one marked with asterisk in whom subtotal resection of right lobe and isthmus was done.
B.M.R.—Basal metabolic rate.
‡Indicates that patients were taking thyroid in dosage of 0.015 to 0.65 gram daily.

Fig. 1.—Photomicrograph of thyroid gland showing the presence of vacuolated cells.

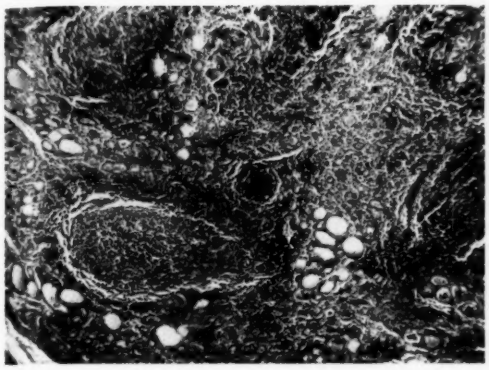

Fig. 2. Photomicrograph showing numerous small thyroid acini with scant colloid and several lymphoid follicles of varying size, some with germinal centers. × 105.

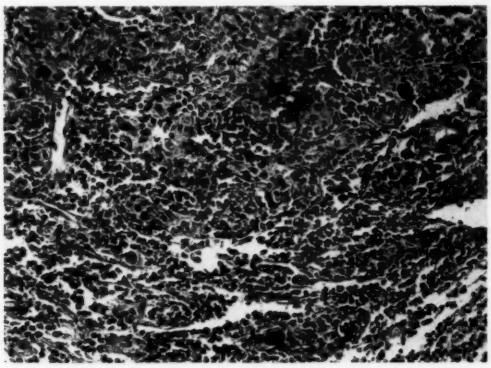

Fig. 3. Photomicrograph showing a few small thyroid acini with diffuse infiltration with lymphocytes and fine connective tissue stroma. × 105.

The Wassermann reaction was negative in the 10 cases in which it was recorded. The basal metabolic rate before operation was below normal in 7 cases, above normal in 3, normal in 1 case, and not recorded in 4 cases. Following operation and before the patient was discharged from the hospital the basal metabolic rate was minus in 4 cases, plus in 1, and not recorded in 8 patients.

Diagnosis. The preoperative diagnosis was nontoxic nodular goiter in 9 cases, adenoma in 2, cystadenoma in 1, Graves' disease in 2, and toxic nodular goiter in 1 case.

Operative findings. At operation, uniform enlargement was noted in 10 cases; in 3 cases of bilateral enlargement one lobe was more enlarged than the other; in 1 case the isthmus was mainly affected and in 1 the isthmus and a single lobe were enlarged. In only 1 case was the gland adherent to the trachea and in only one gland was marked vascularity noted. In 14 cases a subtotal thyroidectomy was carried out, in the remaining case the isthmus and one lobe were removed.

Pathology. Gross: The smallest specimen removed weighed 7 grams, the largest 177 grams; the average weight was 66 grams. As regards consistency, 5 were described as firm, 4 as soft, and 2 as hard. In 8 cases the goiter was described as uniform, while 6 were designated as nodular. The color varied from pearly white through light yellow, yellow, pinkish gray to dark red or brown. In 7 cases colloid was present, while in 1 it was absent; in 7 cases the presence or absence of colloid was not noted.

Microscopic: Uniform changes were noted in 11 of the 15 cases while in the other 4 changes were not uniform. Lymphoid elements were diffuse in 13 cases; in the other 2 there were scattered follicles and slight interacinar infiltration. In the cases with diffuse infiltration there were numerous follicles in all save 1 which showed quite dense interacinar infiltration. The follicles varied in size from 1/3 to 1/30 of a low power field and were considered small in 8 cases, small to moderate in 6, and large in 1 case. For the most part they were round or oval in shape. Germinal centers were present in some or all of the follicles in 14 cases, while in only 1 were there no germinal centers.

Thyroid acini varied from small (1/30 low power field) to fairly large (½ low power field). In 1 case acini resembled those seen in fetal adenoma. In all cases the thyroid acini were round to oval and in 7 some of the acinar cells were in the form of syncytial masses. The acinar cells were flattened in 3 cases, low cuboidal in 2, and fairly high cuboidal in 10. Cytoplasm in all was dull and granular. The nucleus was central or basal and round in all sections, usually with one or more nucleoli. In all glands colloid was present. Many acini contained cellular débris which resembled degenerated acinar cells. The amount of

*All patients were women and all were subjected to subtotal thyroidectomy, except the one marked with asterisk in which subtotal resection of right lobe and isthmus was done.
B.M.R.—Basal metabolic rate.
†Indicates that patients were taking thyroid in dosage of 0.015 to 0.65 gram daily.

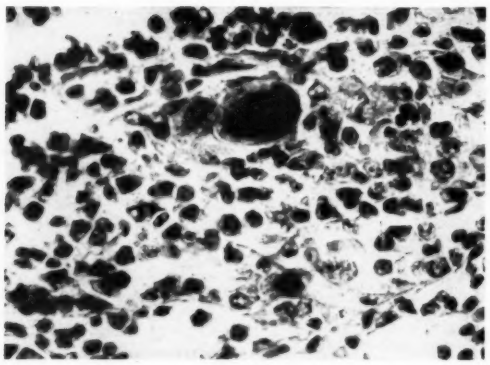

Fig. 4. Photomicrograph showing a pseudogiant cell which is actually a disintegrating thyroid acinus. There is infiltration of lymphocytes and plasma cells. The supporting connective tissue stroma is scant in amount and fine in texture. × 410.

colloid was small in 8, fairly large in 3, and in the other 4 was described as small to fairly large. The color by Masson trichrome stain was orange throughout, and vacuolization of the colloid was present in all instances, varying in degree from slight to marked.

Connective tissue was scant in 9, moderate in 3, and fairly dense in 3. The texture was fine in 12 and fairly coarse in 3 but even when the texture was fine, the trabeculae were dense. Blood vessels were present in the trabeculae in normal numbers in 12, fairly numerous in 2, and numerous in 1 case. In all instances the vessels were small save 1 in which they were designated as small to medium. No true giant cells were seen in any of the sections. In 6 cases no plasma cells were seen; in 6 they were present in small numbers and in 3 numerous. They were found outside the follicles and in the interacinar tissue. Polymorphonuclear neutrophils were seen only in the blood vessels.

Follow-up. We have follow-up records on 13 of the 15 cases and all were examined by both authors. Eight of the 15 patients have been followed for more than 2 years, 5 for more than 3 years, 3 for more than 5 years, and 1 for 6½ years since operation. All patients except 1 showed clinical evidence of hypothyroidism after operation and had lowered basal metabolic rates; the 1 patient had a basal rate of plus 16 and showed mild hyperthyroidism. The basal metabolic rates varied with the amount of thyroid extract administered; it was given after operation to 10 patients. In no case was there a recurrence of goiter. Anemia became marked in 2 patients following operation and in both it was difficult to control. Six patients gained weight, including 4 who were taking thyroid extract.

EVALUATION

The typical case of struma lymphomatosa may be described as follows: A female, 40 to 45 years of age, presents a goiter of long standing which has grown slowly; she complains of weakness, fatigability, slight nervousness, and some pressure symptoms. Examination reveals moderate obesity. The thyroid gland is moderately enlarged, fairly uniform in consistence, and nodular. The basal metabolic rate usually is slightly below normal. The only other laboratory finding of diagnostic value is a slight relative lymphocytosis.

At operation the gland shows fairly uniform enlargement of both lobes and the isthmus; it may be slightly attached to the trachea but usually not to other structures and its vascularity is normal or slightly decreased.

The gross pathological examination reveals a firm, white to yellow or brown nodular thyroid weighing from 60 to 90 grams and with little colloid. Microscopic examination shows the thyroid acini to be atrophic with dull granular cuboidal epithelium. The presence of lymphoid elements is the most striking feature and is in the form of diffuse interacinar infiltration with numerous lymph follicles with germinal centers. Trabeculation usually is fairly marked but otherwise the connective tissue is rather fine and in normal amounts.

This study sheds no light on the cause of this lesion. A history of previous iodine administration was observed in too few of our cases and mentioned too rarely in the cases reviewed to be of etiological significance. A past history of toxicity which might indicate that the lymphoid process resulted from a "burned out" toxic thyroid likewise was rare. Dietary deficiency, suggested as a possible cause of the disease by McCarrison, perhaps warrants further study. With our advance in knowledge of vitamins since his paper was published, some experiments along this line

might be of interest. Struma lymphomatosa certainly seems to be a physiologic or metabolic rather than a neoplastic or inflammatory disease.

All of our patients were subjected to thyroidectomy as were all of the cases collected from the literature except 2, so there is little direct evidence of the course the disease would take if not interrupted by removal of the gland. It is possible only to speculate as to whether without operation the symptoms would progress and more and more of the thyroid acini be destroyed by the increase in lymphoid elements. It is evident from this study that the disease can be controlled by, and does not recur after, subtotal thyroidectomy; that the pressure symptoms and nervousness are relieved after such an operation and that the signs of myxedema can be counteracted by the administration of adequate amounts of thyroid extract to keep the basal metabolic rate within normal limits. Renton, Charteris and Heggie proposed the use of radiotherapy in the treatment of struma lymphomatosa and reported a case of a woman with complaints of goiter and pressure symptoms in which the diagnosis was established by biopsy of the central portion of the isthmus and which was treated with a "radium collar." Their report included a photomicrograph which showed unquestionable struma lymphomatosa. Thirteen days after irradiation was started the goiter had completely disappeared and they reported the patient as "perfectly well" 5 years later. In view of the radiosensitivity of lymphoid tissue and the relative radioresistance of thyroid acini, this procedure may prove to be beneficial in true, microscopically proved cases of struma lymphomatosa. Radiotherapy presumably would not cause the hypothyroidism which follows thyroidectomy and hence would obviate the need of thyroid extract.

CONCLUSIONS

Hashimoto's disease is considered an entity entirely separate and distinct from Riedel's struma both clinically and pathologically. Subtotal thyroidectomy for struma lymphomatosa relieves the symptoms and may be said to cure the disease but the majority of patients after operation develop hypothyroidism of sufficient severity to require the administration of thyroid extract. Two fields for further study have been suggested: the importance of vitamin deficiency as a causative factor and irradiation as a form of treatment.

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MELANOEPITHELIOMA (MELANOSARCOMA, MELANOCARCINOMA, MALIGNANT MELANOMA) OF THE EXTREMITIES

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FOR the purpose of evaluating the methods of treatment and prognosis we have reviewed the clinical and pathological material available in a series of 155 cases in which a diagnosis of melanoepithelioma of the extremity was made at the Mayo Clinic during the 24 years from 1916 to 1939 inclusive. We realize that a lesion of this type is relatively rare and the prognosis has long been recognized as a grave one. In 107 of the 155 cases we found sufficient data on which to base conclusions, and in this group we reviewed the histopathological material and corroborated the original diagnosis. Forty-eight cases of the series were excluded from our study. In 33 of these 48 cases the patients had arrived at the clinic in a hopeless condition; multiple metastatic lesions were present and operation or microscopic verification of the diagnosis was not indicated; in 11 cases the original pathological diagnosis was not substantiated on re-examination of the tissue, and in 4 tissue was not available for confirmation of the original diagnosis.

The purpose of limiting our study to those cases in which the tumor is located in an extremity was so that we may evaluate the relative value of amputation and local excision in the treatment of such lesions. Broders and MacCarty, in 1916, and Farrell, in 1932, reported a series of cases in which lesions of this type were located in all parts of the body and in which the patients were seen at the Mayo Clinic.

HISTORY

In 1806, Dupuytren first described melanoma although some descriptions of this condition in horses appeared in the literature in the latter part of the 18th century. Paget and Virchow recognized that malignant changes took place in moles, and the latter divided these changes into sarcomatous and carcinomatous degeneration. The fact that the cellular picture was so varied stimulated many investigators in their study for the true origin of these tumors. There is still divergence of opinion concerning their origin; some authorities think that they are of epithelial origin. The leaders of this school are Unna and Dawson. The latter has written an excellent monograph on the subject. The belief that melanomas are mesoblastic in origin arises from the fact that many of them appear to be of sarcomatous structure (1, 8). Still other investigators think they arise from the end organs of the peripheral sensory nerves and are neuroectodermal in origin (6, 9).

Since melanoepithelioma is a difficult condition to cure, many forms of treatment have been employed. This same statement, of course, holds true of the treatment of all malignant disease. After a trial of ointments, cautery, and excision, all treatment may be abandoned and the condition considered incurable. Wide excision and block dissection, including the regional glands and amputation of the diseased extremity, have been undertaken without encouraging results. Roentgen and radium treatment frequently have been tried alone or in combination with the procedures mentioned, but even this type of treatment has not proved to be a solution of the problem.

INCIDENCE OF AGE AND SEX

The age and sex distribution in this series of 107 patients has been summarized in Table I; the youngest patient was 12 years of age and the oldest 76 years. The average age was 47.6 years. It is of interest to note that 50.5 per cent of the patients were between 40 and 60 years of age, and the remainder were distributed above and below these ages. The percentage of females affected was 58.9 per cent or 17.8 per cent higher than that of the males which was 41.1 per cent. This is not what we would expect to find if trauma were considered one of the etiological factors. In 33.5 per cent of the cases, however, there was a definite history of some type of trauma or irritation at the site of the initial lesion. Most frequently it resulted from a shoe rubbing, or a nail puncturing, the foot. In the remainder, or 66.5 per cent, trauma was not mentioned in the case history.

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LOCATION AND TYPE OF LESION

The location of the primary lesion in this series of cases is given in Table II. It is obvious that melanoepithelioma has a predilection for the lower extremity, since in this group of patients 76.7 per cent of the primary lesions were located on the legs and the other 23.3 per cent on the arms; 30.9 per cent of the total number, however, were located on the foot exclusive of the toes. The subungual type of lesion comprised only 9.3 per cent of this series and the greater percentage, 6.5 per cent, of these were located beneath the fingernails. The lesions were distributed nearly equally on the right and left sides of the body.

The type of the primary lesion was described variously by the patients, 40 of whom stated that the original lesion was a "mole"; 25 noted the appearance of a tumor first; 20 described a "black, brown, or purple spot"; 12 first noted an "ulcer or abrasion"; 7 a "blood blister"; and 3 stated that the tumor arose from a "callus." At the time of their first visit at the clinic 58, or 54.2 per cent, had an ulcerating lesion at the site of the primary lesion. This in some instances was the result of failure in healing after excision of the primary lesion and in others the result of degeneration in the original tumor. At the time of the original visit, 41 patients had discernible metastatic lesions in addition to the primary lesion which was present.

TABLE I.—AGE AND SEX OF PATIENTS IN VERIFIED CASES OF MELANOEPITHELIOMA OF THE EXTREMITIES, 1916–1939 INCLUSIVE[1]

Age, years	Total		Males		Females	
	Number	Per cent	Number	Per cent	Number	Per cent
10—19	2	1.9	—	—	2	3.2
20—29	13	12.1	4	9.1	9	14.3
30—39	16	15.0	5	11.4	11	17.5
40—49	25	23.4	11	25.0	14	22.2
50—59	29	27.1	13	29.5	16	25.3
60—69	15	14.0	7	15.9	8	12.7
70+	7	6.5	4	9.1	3	4.8
Total	107	100	44	100	63	100
Youngest	12 years		21 years		12 years	
Oldest	76 years		76 years		74 years	
Average	47.6 years		50.5 years		45.6 years	
Sex, per cent	100		41.1		58.9	

[1]Pathological sections and tissue have been re-examined and the previous diagnosis confirmed.

TABLE II.—LOCATION OF PRIMARY LESION IN CASES OF MELANOEPITHELIOMA, 1916–1939 INCLUSIVE

Location	Total		Right		Left	
	Number	Per cent	Number	Per cent	Number	Per cent
Toe, subungual	3	2.8	2	66.7	1	33.3
Toe, other part	15	14.0	9	60.0	6	40.0
Foot (except toes)	33	30.9	11	33.3	22	66.7
Leg	19	17.8	11	57.9	8	42.1
Thigh	12	11.2	8	66.7	4	33.3
Finger, subungual	7	6.5	5	71.4	2	28.6
Finger, otner part	3	2.8	—	—	3	100.0
Hand (except fingers)	2	1.9	—	—	2	100.0
Forearm	6	5.6	4	66.7	2	33.3
Arm	7	6.5	1	14.3	6	85.7
Total	107	100	51	47.7	56	52.3

Metastasis of this lesion apparently occurs through all possible routes. In many of the cases the surrounding tissues were invaded by direct extension; in some cases local stellate extension occurred about the original lesion via the skin lymphatics. Direct metastasis through the deep lymph vessels to the regional lymph nodes and beyond occurred in many cases and in others invasion of the blood vessels was apparent, for the cells had been carried throughout the body by the blood stream which had produced widespread metastasis including the central nervous system and the skin. Metastatic lesions as well as the primary lesion may or may not be pigmented, but in all cases the cellular structure proved the true nature of the lesion.

SYMPTOMS

Enlargement of the primary lesion was the most frequent type of onset noted. Forty-one of the 107 patients complained of some associated pain. As the tumor enlarged, the surface became friable and was prone to bleed when irritated and, as we have stated previously, ulceration occurred in a fair percentage of the cases. In another type the first sign may be an increase in the deposit of pigment without much enlargement of the lesion. Later stellate pigmented growths may appear about the primary lesion. In still another variety the first sign may be metastatic enlargement of the regional lymph nodes and an innocent appearing mole which has undergone malignant changes may be found distally on the extremity. No preexisting lesion is necessary and the first symptoms

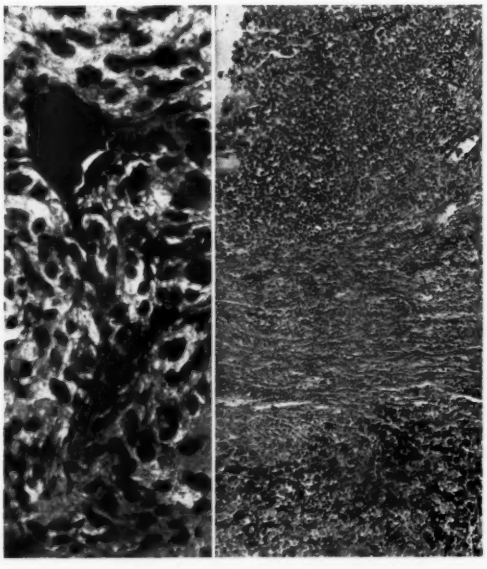

Fig. 1. a, left, Nonmelanotic melanoepithelioma with great variation in the size and shape of the cells and frequent mitotic figures, ×205. The patient died 1 year following excision of a tumor from the heel. b, Areas of pigment and nonpigment bearing cells within the same tumor. Strand and acinar formation is evident in the lower left portion which gives rise to so-called melanocarcinoma type of tumor. ×35.

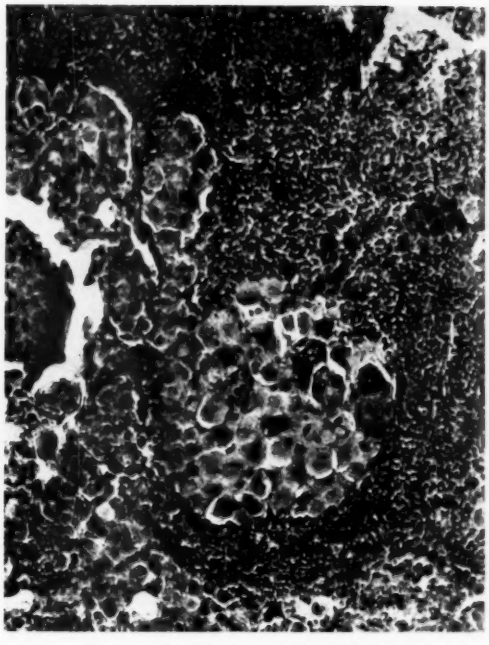

Fig. 2. Metastatic involvement of regional nodes with large round and oval type cells, both pigmented and nonpigmented. ×175. The patient died 1 year following the removal of a tumor and regional nodes.

which are observed in a great number of cases may be the appearance of an entirely new pigmented region or of a tumor which shows progressive enlargement.

DIAGNOSIS

Any new lesion or pre-existing one of the skin which enlarges or ulcerates should be viewed with suspicion. This is especially true of a lesion about the nail bed. If it is pigmented, a presumptive diagnosis is easily made. However, in the nonpigmented type of melanoepithelioma the true nature of the lesion is not evident until microscopic examination of the tissue has been made.

Differential diagnosis. The final diagnosis of melanoepithelioma rests with the pathologist following his study of the histological picture. However, several clinical entities may be confused with it; they are benign pigmented moles, blue nevus, lentigo, verruca senilis, pigmented basal cell epithelioma, melanotic carcinoma of the breast and hemorrhage, any one of which may simulate melanoepithelioma.

HISTOLOGICAL PICTURE

Little can be added to the knowledge of the histological picture of these tumors that has not already been brought out by Dawson in his excellent monograph. The cells themselves are pleomorphic and vary from round ones to spindle-shaped ones as shown in Figure 1,a. Branched and polyhedral cells may be present and nearly always their size varies greatly. The nuclei are large, vesicular, stain only lightly, and frequently contain mitotic figures. The cells contain a variable amount of pigment; the basal layers contain the most. These layers may be filled completely or even appear to be bursting with it, and the pigment also may be seen deep within the subcutaneous tissue. In tumors of the nonmelanotic type, pigment was not seen although the cellular structure was characteristic in every other respect. Within the same tumor may be seen regions of deep pigmentation or regions completely devoid of pigment as demonstrated in Figure 1,b. The cellular arrangement may take one of several forms. They may be arranged in sheets of cells with little intercellular substance

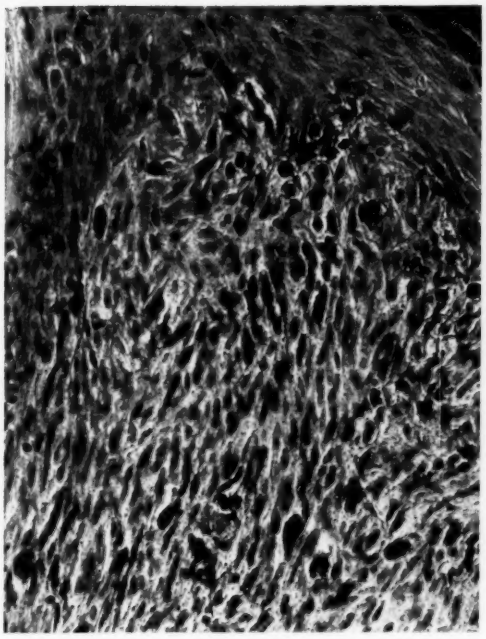

Fig. 3. Spindle cell or sarcomatous type of melanoepithelioma with only light pigmentation. ×222. The patient is living without evidence of metastasis 2 years following amputation of an arm.

Fig. 4. Strand and acinar-like arrangement of cells or so-called melanocarcinoma. ×94. The patient is living without evidence of metastasis 8 years following amputation of a toe.

and no definite pattern; the predominant cells may be round as shown in Figure 2, or spindle-shaped as shown in Figure 3. In other tumors the cells form in strands and have an acinus-like arrangement which gives rise to the adenocarcinomatous appearance of some of these tumors, as shown in Figures 1,b and 4. Perivascular and perilymphatic masses of cells are evident in some tumors and not infrequently malignant cells are included within the lumen of blood vessels and lymphatic spaces. Within the same tumor the cellular structure and arrangement may differ and vary from a carcinomatous nature to the spindle cell sarcomatous type of tumor; usually, however, only one type of cellular picture is predominant. As a rule metastatic lesions are of the same cellular structure and pattern as the primary tumor, but they may or may not be pigmented. In the early stages it may be difficult to distinguish the tumor from a benign pigmented cutaneous lesion, but the true invasive nature of the cells of melanoepithelioma may be determined by a careful study of the tissue, as demonstrated in Figures 5 and 6.

TREATMENT

In 50 of the 107 cases some form of treatment had been given elsewhere. Some of the more common methods mentioned by the patients cannot be included as proper means of treatment, namely, heat and massage, ointment, pastes, caustics, inadequate cautery and electrodesiccation, and curettement of ulcers. The types of treatment which have been employed at the clinic and those used elsewhere are listed in Table III. In far the greatest number of cases either a wide excision of the local lesion including even metastatic lesions in nodes or amputation of the affected digit or extremity was employed. In a few of the cases amputation was done as a palliative measure because of the distressing nature of the primary growth.

RESULTS AND PROGNOSIS

To analyze and obtain survival rates in a study of a condition, such as melanoepithelioma, in which the nature of the lesion, the time of institution of treatment, and the types of treatment are so varied, is a difficult task. On the extremities where the lesion is so open to inspection and the

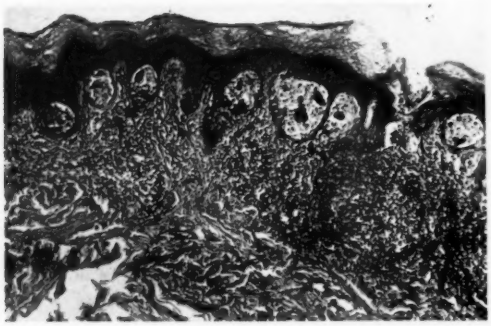

Fig. 5. Tissue from a lesion which had been excised from the foot of a patient who is living without evidence of metastasis 6 years following operation. ×471. Examination with high power magnification demonstrated infiltration of malignant cells into muscular tissue.

onset of symptoms points to the actual onset of malignant changes, the basing of the survival rate on the time the tumor actually began should be considered. The proof of malignancy, however, awaits biopsy. In this study, the 3 and 5 year survival rates have been computed from the onset of symptoms and also from the time that treatment was instituted.

In a series as small as this one, if the cases were divided in accordance with all the detailed types of treatment employed, the number in each group would be too small a one on which to base any conclusions. For that reason we have divided our cases into only three groups: (1) those in which surgical treatment had not been given; (2) those

TABLE III.—TREATMENT OF MELANOEPITHELIOMA, 1916–1939 INCLUSIVE

Treatment at clinic	Total	Previous treatment elsewhere	
		Excision	Amputation
No treatment	6	1	2
Lead only*	2	2	—
Irradiation only*	15	10	1
Excision of lesion†	29	9	1
Excision of lesion and metastatic nodes†	32	16	2
Amputation†	23	6	—
Total	107	44	6

*Lead phosphate was administered in 13 cases. In 2 cases this was the only form of treatment; in 1 case the only other treatment was irradiation; this case is listed under the heading, irradiation only. In 1 of the 13 cases excision of the primary lesion was performed; in 8, excision of the primary lesion and metastatic nodes and in 1, amputation.

†With or without irradiation; irradiation was employed in 12 cases of excision of the primary lesion, in 28 cases of excision of the primary lesion and metastatic nodes, and in 15 cases of amputation.

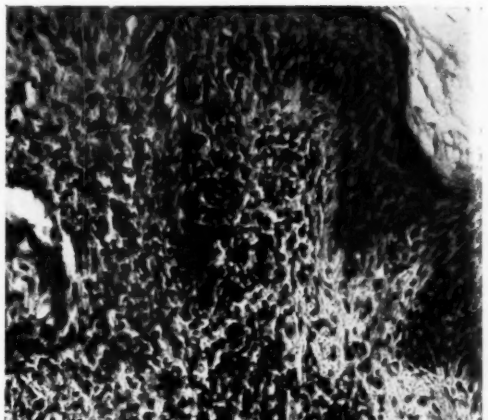

Fig. 6. Transition from normal to malignant epithelium and deep penetration of malignant cells into subcutaneous tissue. ×184. The patient is living one year following excision.

in which amputation had been performed; and (3) those in which local excision of the primary lesion and of local recurrences was performed with or without excision of the regional nodes.

The computed survival rates are given in Tables IV and V. It is interesting to note that in all the highest percentage of survivals occurred following excision. Cases 1 and 2 in this paper are examples of such survival. Many of the amputations were performed in cases in which the lesion was more extensive while excision was carried out incidentally, at times, when an operation for some unassociated lesion was being done. This accounted to some extent for the better results obtained in the group in which excision was performed, but after all factors have been taken into consideration, it is felt that when it is possible wide excision of the lesion and of any suspicious nodes offers the patient as favorable an outlook as does amputation. In those cases in which a digit is involved local excision is not feasible and amputation is the procedure of choice.

In only 1 case (Case 3) in this series did the melanoepithelioma respond to irradiation in the

opinion of the radiologists. In a condition with as grave a prognosis as that which we have in melanoepithelioma, every patient certainly is entitled to even the questionable benefits that may be derived from irradiation with or without associated operation.

In this type of malignant neoplasm, as in no other, the unknown equation of individual resistance to a tumor of high grade of malignancy appears to play a part. Several patients (Case 4 for example) survived a long period after repeated excision of the local and regional recurrences.

REPORT OF ILLUSTRATIVE CASES

CASE 1. A woman, aged 24 years, was seen at the Mayo Clinic on August 22, 1922, at which time she stated that since birth she had had a somewhat elevated papillomatous lesion on the lateral aspect of the left thigh and that it had been increasing in size during the past 10 years with more rapid growth during the last 2 years. Examination revealed a tumor, about 3 centimeters in diameter, which had become a soft pedunculated papillomatous mass. Excision was performed on August 25, 1922, and pathological examination of the tissue removed revealed a typical melanoepithelioma. Because it was felt that this lesion was in its early stages and excision had been complete, no further treatment was advised. In reply to an inquiry letter, which was dated August 19, 1940, the patient stated that she was well, did not have any sign of recurrence of the tumor, and had been well during the past 18 years.

CASE 2. A woman, aged 57 years, was examined at the Mayo Clinic on February 4, 1921. She stated that she had had a blood blister on the palmar surface of the web of the thumb of the left hand and that, in 1919, she had removed this hard, black lesion with a plaster, but it had recurred in September of that year. The lesion then had been removed by means of an electric needle and 6 roentgen treatments had been given. Furthermore, the following year the tumor had recurred and she had sought further treatment.

Because of the suspicious nature of the lesion biopsy was performed at the clinic and the pathological examination verified the clinical diagnosis of melanoepithelioma. On February 10, 1921, a wide excision of the tumor was performed after which a course of radium treatment was given. In reply to an inquiry received on August 21, 1940, the patient stated that she was living and without known metastasis, 19 years following treatment at the clinic.

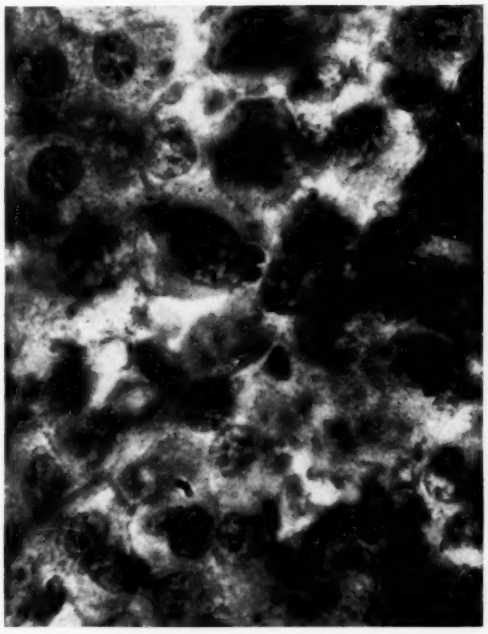

Fig. 7. Case 3. Large round and oval cells with little intercellular substance and no pigment. ×850.

TABLE IV.—THREE AND 5 YEAR SURVIVAL RATES FROM TIME THAT TREATMENT OF MELANOEPITHELIOMA OF THE EXTREMITIES WAS INSTITUTED

Group	Total*	Traced	Lived 3 or more years following treatment		Total*	Traced	Lived 5 or more years following treatment	
			Number	Per cent of traced cases			Number	Per cent of traced cases
No surgical treatment	6	6	0		6	6	0	
Amputation	23	22	8	36.4	20	19	4	21.1
Excision	67	63	25	39.7	60	57	17	29.8
Total	96	91	33	36.3	86	82	21	25.6

*Inquiry as of January 1, 1941. The 3 year group comprises the patients treated 3 or more years prior to the time of inquiry, that is 1937 or earlier; the 5 year group comprises those treated in 1935 or earlier.

TABLE V.—THREE AND 5 YEAR SURVIVAL RATES FROM TIME OF ONSET OF SYMPTOMS OF MELANOEPITHELIOMA OF THE EXTREMITIES

Group	Total*	Traced	Lived 3 or more years after onset		Total*	Traced	Lived 5 or more years after onset	
			Number	Per cent of traced cases			Number	Per cent of traced cases
No surgical treatment	7	7	3	42.9	7	7	2	28.6
Amputation	26	23	15	65.2	25	23	9	39.1
Excision	68	65	45	69.2	65	62	28	45.2
Total	101	95	63	66.3	97	92	39	42.4

*Inquiry as of January 1, 1941. The 3 year group comprises the patients who had onset of symptoms 3 or more years prior to the time of inquiry, that is, 1937 or earlier; the 5 year group comprises those who had onset of symptoms in 1935 or earlier.

CASE 3. A woman, aged 23 years, was seen at the Mayo Clinic on February 20, 1920, at which time she stated that she had noticed a tumor of the right calf and a swelling of the right groin for 2 months prior to admission and that these had been enlarging gradually. The nevus was removed from the calf and the pathological examination revealed melanoepithelioma (Fig. 7). On February 26, 1920, the enlarged and normal lymph nodes were dissected from Scarpa's triangle on the right, and metastatic involvement was found. Subsequently, the lesion in the calf which was removed on March 18, 1920, recurred and still later that in the right inguinal region which was removed on August 12, 1920. After this last recurrence the patient received intensive roentgen and radium treatment to the leg and groin. The patient returned to the clinic in 1936, at which time she had no complaint except for tenderness of the regions to which irradiation had been directed. At this time the radiologist made a note to the effect that the tumor apparently was radiosensitive. In a reply to an inquiry received on August 21, 1940, the patient stated that she had been in good health and did not have any evidence of recurrence 20 years after the institution of treatment.

In this case the prognosis apparently was hopeless at the time treatment was instituted, but in spite of this the patient survived and enjoyed 20 years of life. The fact that recurrence of the lesion took place following each excision but did not do so following irradiation would lead us to believe that the latter had been the arresting procedure.

CASE 4. A woman, aged 47 years, was first seen at the Mayo Clinic on April 10, 1915, at which time she stated that she had noticed a mole on the calf of her left leg for the past 5 years; that about 1 year previously it had enlarged and was removed by her physician, but during the recent months a lump had recurred at the site of excision.

Wide excision of the tumor of the calf was performed and on the same day pathological examination of the tissue revealed melanoepithelioma (Fig. 2). Healing occurred promptly and the patient was not seen again until May 4, 1916, at which time she returned to the clinic because of recurrence at the site of operation. Removal was carried out again and the pathological examination revealed the same condition. Three months later the patient again reported at the clinic with evidence of enlarged right inguinal glands; these were removed and the pathological examination again revealed melanoepithelioma. At this time an intensive course of radium and roentgen treatment was given to the groin. The patient died on May 27, 1927, 12 years following her first admission at the clinic.

In this case we have an illustration of the length of life possible after metastasis has occurred. Although the treatment given did not cure the patient, it did increase the length of her life.

CONCLUSIONS

We have reviewed those cases of melanoepithelioma of the extremities which were encountered at the Mayo Clinic during a 24 year period.

It is apparent that if treatment had not been instituted the patients would have died, whereas 29.8 per cent of the patients who were treated by excision survived 5 years or more from the time treatment was instituted. This group included many cases in which the lesions were small and the patients were seen during the early stages of the disease.

In those cases in which the lesion was more extensive and of long duration amputation was the most common type of treatment, yet in this group there was a 5 year survival rate of 21.1 per cent from the time treatment was instituted.

None of the patients in that group in which irradiation was the only form of treatment survived 3 years from the time treatment was instituted at the clinic. Irradiation was employed in conjunction with operation in numerous cases, in those cases in which the patient refused an operation and in those in which the lesion was inoperable. This form of treatment should not be condemned as further advancement in the science of radiology and its clinical application may prove it of more benefit than is now apparent.

Melanoepitheliomas may be present for long periods of time before the seriousness of their nature is determined or recognized, and their condition may be activated by meddlesome treatment. Therefore, in the authors' opinion the treatment of choice for melanoepithelioma is wide excision with removal of regional lymph nodes or amputation. In cases in which tumors do not appear to be increasing in size or showing evidence of ulceration, wide local excision would appear adequate.

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SCHWANNOMAS (NEURILEMOMAS) IN THE HEAD AND NECK

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THE present study is based on an analysis of 10 cases of schwannoma arising in the tissues about the head and neck; these were observed at the Memorial Hospital from 1936 through 1942. Such neoplasms are known to occur in almost every part of the body, but when situated in the head and neck they present special diagnostic and therapeutic problems which seem to us to warrant a separate discussion.

Definition. A specific form of encapsulated and essentially benign tumor of the sheath of peripheral nerves was first described in 1908 by Verocay (35, 36) who introduced the term "neurinoma." Mallory proposed the name "perineurial fibroblastoma" for this tumor to designate an origin from the fibroblast. The term "schwannoma" (from the sheath of Schwann) has been widely used, apparently because the bulk of available evidence favors the schwannian theory of histogenesis. Since there is a difference of opinion as to whether this tumor is of schwann cell (ectodermal) or fibroblastic (mesenchymal) origin, and since it is generally agreed that this is a tumor of the neurilemma, then Stout's contribution—"neurilemoma"—appears reasonably specific. Before Stout's publication, Ewing had suggested the name "neurilemnoma" for these tumors.[1]

ETIOLOGY

Incidence. Schwannoma is a rare tumor. Its general incidence can be judged by the fact that it occurs only about 1/50th as frequently as cancer of the lip. The 10 cases (in the head and neck) herein reported comprise 43 per cent of all schwannomas (23 cases) encountered at the Memorial Hospital during the 6 year period—1936 through 1942. In most other reports on this tumor, the proportion arising in the head and neck is less than in our series. In Stout's series of 50 cases—the largest collection of schwannomas to appear in the literature—only 26 per cent were situated above the level of the clavicle. The higher proportion in this location found at the Memorial Hospital may possibly be due to the relatively large number of patients with all varieties of head and neck tumors—about 1600 new cases yearly—admitted to our clinic.

In our series, the tumors were distributed as follows: neck, 7 cases; soft tissues of the nose, 1 case; retropharyngeal area, 1 case; retrotonsillar area, 1 case. The preponderance of origin in the neck, as compared to the head, has been noted by others and can be explained by the relatively large number of peripheral nerve trunks grouped in this area. Askanazy, Figi, and Stout have each reported single cases of schwannoma in the retropharyngeal, retrotonsillar, and nasopharyngeal areas, respectively. Other authors have reported instances of this tumor in such regions as the eye (8, 18), orbit (5, 6, 28, 29), eyelid (12), maxillary sinus (33), floor of mouth (4), tongue (3, 12, 16, 17, 33), hard palate (2, 22, 33), larynx (15, 30, 32, 33), and salivary glands (33).

Two of our tumors (Cases 1 and 7) had their origin from the phrenic nerve. Figi, Freifeld, and Stout have described schwannomas which arose from the cervical sympathetic nerves. Sekiguchi and Oije and Cutler and Gross have each encountered a schwannoma with origin from the vagus nerve. The tendency of this tumor to originate in the 8th cranial nerve is well recognized by neurosurgeons.

Age and sex. In our series, the oldest patient was 68 years and the youngest 23 years old at the time of admission. These tumors, however, may appear at any age. Stout has described 4 cases in which the tumors apparently became evident during the first year of life. Both sexes were equally affected. In our series, there were 5 males and 5 females.

Causative factors. An analysis of our cases reveals no evidence of a common causative factor. Many observers have commented on the frequent association of schwannomas with the multiple neurofibromatosis of von Recklinghausen. That there was no instance of this recorded in our series is probably of little significance since the records give no evidence that the examiner particularly looked for neurofibromatosis. The association of pigmented naevi (Case 2), a ganglion (Case 9)

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[1] Other terms encountered in the literature were peripheral glioma, lemmoma, encapsulated neurofibroma, neurinoma sarcomatodes, false neuroma, and fibroma molluscum.

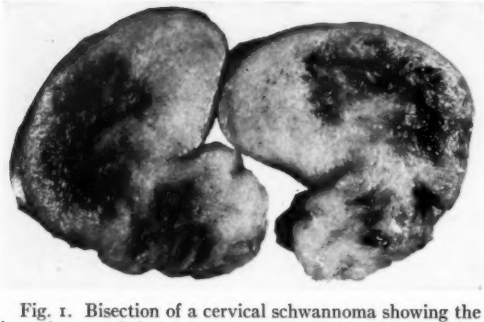

Fig. 1. Bisection of a cervical schwannoma showing the irregular mottled appearance and necrosis. Note cavity formation. This tumor was located at the carotid bifurcation and was of phrenic nerve origin (Case 7).

and a synovioma (Case 3) appeared to be merely coincidental.

PATHOLOGY

Gross pathology. All the tumors in this collection were encapsulated. They varied from 1.5 centimeters to 7 centimeters in greatest diameter. The majority of the specimens were globular or fusiform and smooth, although in a few instances the surface was nodular and even distinctly lobulated. The consistency was soft and sometimes fluctuant; this characteristic may be explained by the cystic degeneration that these neoplasms usually undergo. Occasionally, a growth was firm and fibrous.

The cut surface was glistening and revealed a multiplicity of patterns. Most often irregular mottled areas were seen, ranging from pink to yellow to pearl gray in color. Occasionally, these patches were arranged in whorls. The central portion of the tumor was almost always necrotic. Hemorrhages were frequently scattered throughout, especially beneath the capsule (Fig. 1). Areas varying from cystic degeneration to spaces containing fluid were encountered, and in such specimens definite fluctuation was elicited before the tumor was cut.

The tumors of the neck presented distinctive and uniform anatomic features. They were sharply demarcated from the surrounding structures. With the exception of one tumor which was located in the supraclavicular area, the others were situated beneath the upper one-third of the sternocleidomastoid muscle and usually anterior to the carotid vessels. Frequently a large nerve was seen to disappear into the tumor; most of the nerve fibers, however, could often be stripped away from the capsule. The smaller tumors confined themselves to this location, but the larger tumors extended beyond this area to the mastoid tip, the pharyngeal wall, and even to the transverse processes of the adjacent cervical vertebrae.

The capsule was well supplied with blood vessels which did not penetrate into the substance of the tumor, while the vascularity of the tumor was generally poor.

Histopathology. For many years, it has been customary to divide the histologic picture of this nerve sheath tumor into the type A and type B tissues of Antoni. This classification is so specific and descriptive as to warrant its continued use.

Type A tissue is characterized by a reticulum of fine, long fibers which pass between the cells. The cells and their nuclei are elongated and cytoplasmic processes stream out to form a network. The intracellular fibers are in a parallel arrangement, while the elongated cell nuclei are lined up

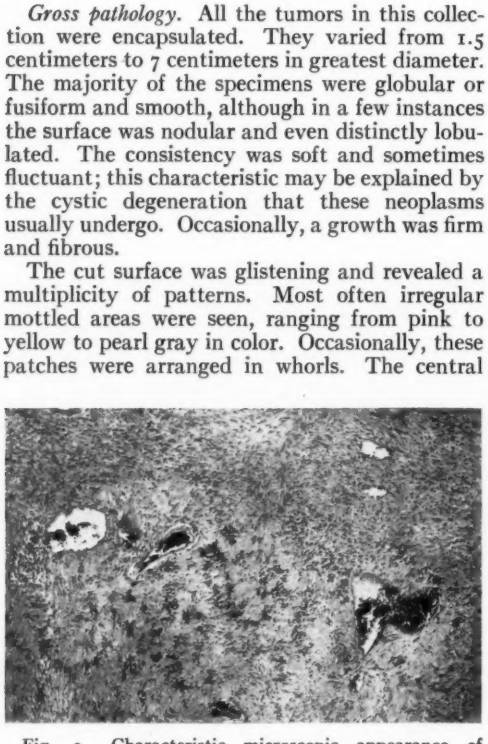

Fig. 2. Characteristic microscopic appearance of schwannoma. The nuclei are lined up at the opposite end of the fibers, producing typical palisades (Antoni type A tissue).

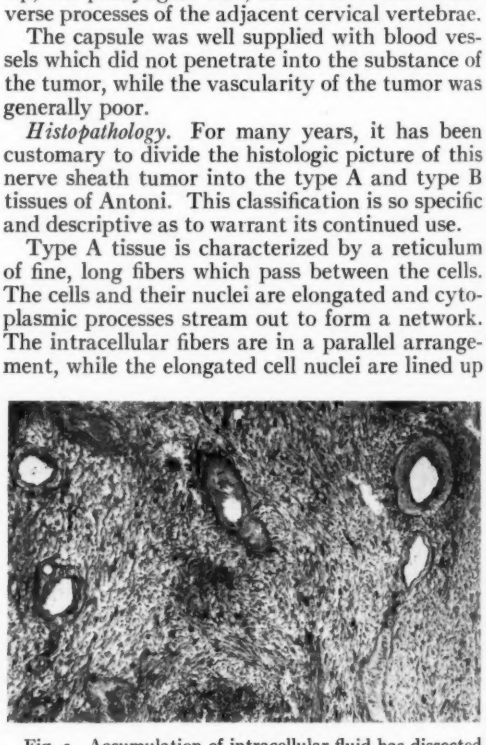

Fig. 3. Accumulation of intracellular fluid has dissected the fibers apart, breaking up the palisades. Note the thick walled blood vessels, one of which contains a thrombus (Antoni type B tissue).

at the opposite end of the fibers. This produces a palisading pattern, which is so characteristic of schwannoma (Fig. 2). The cells and fibers also form whorls.

Areas of fibrosis and necrosis are invariably encountered in this portion of the tumor. Hemorrhage, too, is a common occurrence, as well as thromboses within thick walled blood vessels. This necrotizing process produces areas in which fibers have disappeared and only cells remain, or areas in which the reticulum is devoid of cells.

In the type B tissue, there is no orderly arrangement of cells and fibers, and therefore no palisading of nuclei is seen. This phase is characterized by an accumulation of intracellular fluid and the appearance varies from one of edema (Fig. 3), which dissects the tissue apart, to microcystic degeneration (Fig. 4).

Specific staining techniques for the identification of axis cylinders were not carried out in any of our specimens.

Although the schwannoma has generally been considered a benign tumor, atypical areas containing hyperchromatic and pleomorphic cells and suggestive of early malignant changes were observed in Cases 4 and 8 (Fig. 5).

Histogenesis. The histogenesis of these tumors has been a subject of controversy for many years. One group of investigators, led by Penfield, contends that the tumor is of fibroblastic origin, and therefore, a mesenchymal neoplasm. On the other hand, the hypothesis first proposed by Verocay (35, 36) and supported by Masson states that the tumor arises from the cells of Schwann and that it is, therefore, an ectodermal neoplasm.

Those who support the connective tissue theory argue that the tumor cells resemble fibroblasts

Fig. 4. Further edema has produced microcystic degeneration. Palisades have been completely destroyed (Antoni type B tissue).

morphologically, and that only fibroblasts can produce collagen. Recently, however, Masson has produced experimental schwannomas and has been able to trace both the experimental and spontaneous tumors back to the schwannian syncitium. Masson, and Murray and Stout (24, 25) have demonstrated by means of tissue cultures that the cells of these specific nerve sheath tumors are morphologically and physiologically similar to the cells of Schwann. Also, Murray and Stout have cultivated the tumor *in vitro* and demonstrated the derivation of reticulin fibers from the cells of Schwann.

The bulk of available evidence, therefore, appears strongly to favor the schwannian theory of origin.

SYMPTOMS AND CLINICAL COURSE

The tumors are probably always of long duration when first discovered. In 5 of our cases,

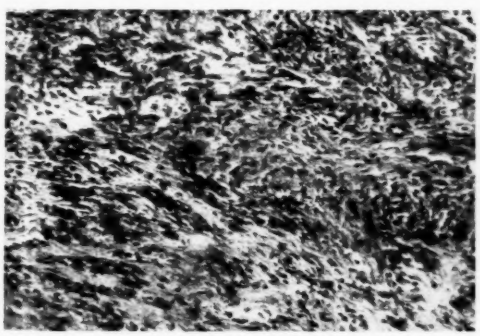

Fig. 5. A schwannoma which was suspected of early malignant transformation because of atypical areas shown above. The cells are hyperchromatic and pleomorphic; there is no orientation between fibers and cells. This tumor was clinically and anatomically benign (Case 4).

Fig. 6. Tissue which was obtained by aspiration biopsy of a retrotonsillar schwannoma. Palisading pattern is definite. The structure at the left end of the field is part of a blood clot, to which the tumor tissue is seen to be attached (Case 10).

according to the patients' histories, the growths had been present for from 6 to 10 years, and in 1 case for 1 year. In the 4 remaining cases, the patients stated that the tumors had been noted 5 months, 8 months, 5 months and 3 weeks, respectively. In the latter group, since the growths were all 2.5 to 5 centimeters in greatest diameter, the patients' statements must be considered unreliable, and one must conclude that schwannomas are probably slowly growing and of long duration when first discovered.

The most common and often the only symptom is the physical presence of the tumor. In our series, over one half of the patients had no other complaint on admission. Since the tumor originates in nerve tissue, one might logically expect pain to be frequent and characteristic, but in the present series this symptom was present in only 3 cases and in only 1 case was it severe. When present, pain appears to be due to pressure of the tumor on adjacent nerves, rather than to the nerve of origin. Another symptom which might be expected was mechanical obstruction to swallowing. This was encountered in our 2 pharyngeal cases (Cases 3 and 10).

A Horner's syndrome was encountered once in our series (Case 2) and persisted despite complete removal of the cervical tumor. This may be attributed to pressure by the tumor on the cervical sympathetic plexus with irreparable nerve damage. One may also speculate whether such a tumor may have had its origin from a cervical sympathetic nerve, even though the nerve could not be identified as part of the tumor. Schwannomas with origin from the cervical sympathetic nerves have been described by Figi, Freifeld, and Stout. A temporary Horner's syndrome occurred as a postoperative complication following excision of a cervical tumor (Case 9). This phenomenon has been encountered by others and can be attributed to tissue changes or possibly to trauma following surgical manipulation.

On physical examination the tumors were always found to be single, circumscribed, soft, movable and not tender. In our cases, they possessed no characteristic features differentiating them from the average encapsulated clinically benign tumor.

The clinical course of schwannoma is apparently benign even without treatment. Since the diagnosis cannot be made except by histological examination, it naturally follows that in all reported cases the tumors have been excised. There is no way of knowing what would happen if the growths are left untreated, except if the diagnosis is made by aspiration biopsy. So far, no aspirated tumor has been observed for any long period without treatment. In our Case 10 the diagnosis was made by aspiration biopsy, but the patient has been followed only 1 year, during which time there has been no apparent change in the lesion or symptoms. In Case 7, the tumor had been noted 10 years previously and yet it had reached a size of only 5 centimeters in diameter on admission, and there was no complaint except the presence of the mass.

DIAGNOSIS

In our series, the diagnosis of schwannoma was not made clinically in a single instance before a microscopic report was returned. In the average case of schwannoma of the neck, the long duration of the tumor, the absence of any growth in the mouth or pharynx which might point to a cervical metastasis, and the discrete soft character of the tumor mass should lead the experienced clinician to a tentative diagnosis of a benign primary tumor. Further than that, no one can proceed on the clinical aspects alone. The possible varieties of discrete benign soft part tumors which can occur in the head and neck are so numerous that little is to be gained by an attempt at a more exact clinical diagnosis than that a given tumor is encapsulated and probably benign.

Differential diagnosis. In our series, 7 of the tumors occurred in the neck, and in these the following tentative clinical diagnoses had been made before aspiration biopsy or operation, respectively: lipoma, submaxillary salivary gland tumor, cervical lymph node metastasis, lymphosarcoma, neurogenic sarcoma, carotid body tumor and cystic hygroma.

As has previously been mentioned, an attempt at exact differential diagnosis by clinical measures alone and without biopsy of discrete soft part tumors of the head and neck is largely an academic exercise and is, furthermore, dangerous to the welfare of the patient if taken too seriously. Good oncologic practice demands first that all clinically demonstrable foci of a growth be discovered and next that tissue be obtained from the most readily accessible and safest site. Until a histological section has been examined under the microscope, the diagnosis is only tentative.

Some authors (13, 27) have commented on the similarity between schwannomas in the region of the carotid bifurcation and carotid body tumor. Both forms of tumor are rare. Carotid body tumors can seldom be diagnosed clinically except by one characteristic feature, that is, *pulsation of the carotid artery over the tumor itself*. This pulsation is due to the deep origin of carotid body tumors in

the crotch of the carotid bifurcation and the tendency of these tumors to grow inward and to push the artery outward. Since schwannomas supposedly arise from the sheaths of the nerves, it has been thought that mobility in the horizontal plane and fixation in the vertical plane are important diagnostic signs and that for this reason, they might also be confused with carotid body tumors which are supposedly characterized by these same limitations in mobility. The practical importance of these diagnostic signs, in our opinion, have been somewhat overemphasized.

Aspiration biopsy. This procedure was used as a means of preoperative diagnosis in 6 cases and a positive report was given by Dr. Fred Stewart, pathologist of the Memorial Hospital, in 5 cases. In the 1 instance in which a single aspiration biopsy gave a negative result, it is probable that further attempts would have revealed the histological character of the tumor, as was demonstrated in Case 5. The practical significance of aspiration biopsy in the diagnosis of cervical tumors cannot be overemphasized. The importance of knowing whether one is dealing with a benign growth like schwannoma, metastatic cancer, carotid body tumor, or a primary localized malignant tumor is obvious. It is only by aspiration biopsy that an accurate preoperative diagnosis can be made in clinically doubtful cases.

This procedure is of special value in the retropharyngeal and retrotonsillar tumors, in which operative intervention may be hazardous. A retrotonsillar schwannoma may simulate a primary tumor of the tonsil. One of our patients (Case 10) was subjected to x-radiation and tonsillectomy before aspiration biopsy finally revealed the character of the tumor (Fig. 6).

TREATMENT

In all the cases previously reported, the tumors have been excised and the diagnosis made first histologically on the surgical specimen. Even though it may be comforting to the surgeon and the patient that the procedure turned out to be the proper one and permanently successful, nevertheless, under such circumstances, the treatment in any given case was not actually selected for schwannoma but rather for a tumor of unknown or at least uncertain character. It is probable that the same surgeon had also excised other tumors which to him appeared identical, but which unfortunately proved to be metastatic cancer or some other growth best not treated by local excision. At the present time, the histological character of most accessible tumors can be determined by aspiration biopsy and the most suitable form of treatment selected on the basis of that information.

When the certain diagnosis of schwannoma has been made, the management of the growth should be decided after a consideration of the known anatomy and clinical course of the tumor. If it produces a visible alteration in the surface contour, the growth should be locally excised (enucleated) for psychologic and cosmetic reasons.

If the patient has any undue fear or other objection to surgery, one is hardly justified in urging operation. Second, when the tumor is situated in a less accessible area, such as the pharynx, surgical removal in certain cases will be attended by definite risk, especially in older subjects. Such a situation is illustrated by our Case 10. In this patient the tumor bulged in the tonsillar region with a marked pulsation over its apex. The patient was in poor general condition and had marked hypertension. Under such circumstances even though the patient prefers an operation, the prudent surgeon is justified in deferring the procedure indefinitely with the confidence that in any case, progress of the growth is slow and malignant degeneration improbable.

Surgical excision was performed in all of our cases except 2—the retropharyngeal and retrotonsillar cases—in whom operation was considered to be unjustifiably hazardous for these benign tumors with minimal symptomatology. No technical difficulties were encountered in those operated on. In every case, the mass was encapsulated and enucleation was performed with ease, even in those instances in which the tumor was adherent to the carotid vessels or to the intervertebral lamina. The vascularity of this neoplasm was a characteristic of some practical significance. The capsule was well supplied with blood vessels which did not penetrate into the substance of the tumor. If the capsule was first incised, no bleeding was encountered on enucleation of the mass. When the capsule had been torn or when an attempt was made to enucleate the tumor without preliminary incision of the capsule, troublesome bleeding followed.

Supplementary roentgen therapy was given one patient (Case 8) because the tumor cells were hyperchromatic and pleomorphic (Fig. 5). Another patient received postoperative radium element pack therapy because of the possibility that tumor tissue may have been left high in the neck posterior to the carotid sheath (Case 2). As our familiarity with the behavior of schwannomas has increased, we now believe that in retrospect, these 2 cases should not have received radiation therapy. Two of our patients (Cases 3 and 10) were

TABLE I.—TABULATION OF CASE REPORTS

Case No. Initials Age Sex	Date of admission	Clinical features	Size of tumor (greatest diameter) cm.	Aspiration biopsy	Treatment	Subsequent course	Remarks
1 D. M. 35 M	5- 9-36	Mass in neck of 6 months' duration	4	Not done	Radium and roentgen therapy, followed by surgical excision	No recurrence after a 7 year follow-up	Simulated a carotid body tumor. *Phrenic nerve origin*
2 C. K. 23 M	3-17-37	Mass in neck of 5 months' duration. History trauma. Horner's syndrome	3	Not done	Excision, followed by radium element pack therapy	No recurrence after 5 year follow-up. Persistence of Horner's syndrome	Simulated a carotid body tumor. *Associated tumor:* numerous pigmented nevi
3 E. G. 37 F	4-17-39	Pain on swallowing of 1 years' duration. Retropharyngeal mass	4	Positive	Observation	No enlargement after 3 year follow-up. No recurrence of synovioma	Received roentgen therapy before admission. *Associated tumor:* synovioma of abdominal wall
4 J. W. 45 M	11- 6-39	Swelling over nose of 8 months' duration	1.5	Not done	Excision	No recurrence. Died 1 year following excision (peritonitis following hernia operation)	Microscopic examination suggestive of early malignant changes
5 M. L. 35 F	12-28-39	Mass in neck of 5 months' duration	5	Positive (after third aspiration)	Excision	No recurrence after 3 year follow-up	Simulated a carotid body tumor
6* H. M. 65 M	3-26-40	Mass in neck of 7 years' duration. Pain over tumor of 4 months' duration	7	Positive	Excision	No recurrence after 2 year follow-up	Dumbbell shaped tumor extending to cervical vertebrae. Roentgen therapy before admission
7 H. T. 36 M	11-28-40	Mass in neck of 10 years' duration	5	Negative	Excision	No recurrence after 2 year follow-up	Simulated carotid body tumor. *Phrenic nerve origin*
8 L. D. 68 F	4-13-41	Mass in neck of 3 weeks' duration	4	Not done	Excision, followed by roentgen therapy	No recurrence after 18 months' follow-up	*Possible origin from brachial plexus.* Microscopic examination suggestive of early malignant changes
9‡ R. G. 52 F	4-21-41	Mass in neck of 6 months' duration. Pain in head and neck of 2 years' duration	4	Positive	Excision	No recurrence after 18 months' follow-up. Headache unrelieved	Simulated carotid body tumor. Temporary postoperative Horner's syndrome. *Associated tumor:* ganglion of wrist
10 D. H. 59 F	3-10-42	Pain on swallowing of 6 years' duration. Retrotonsillar mass	4	Positive	Observation	No enlargement after 1 year follow-up	Roentgen therapy and tonsillectomy before nature of tumor was established by aspiration biopsy

*Reported by courtesy of Dr. George T. Pack. ‡Reported by courtesy of Dr. Lloyd C. Craver.

subjected to roentgen therapy before coming to the Memorial Hospital and in Case 1 the patient received preoperative radium and roentgen therapy, but tumor regression was not observed in any of these patients.

Like all tumors of nerve tissue origin, schwannomas are apparently highly radioresistant and therefore radiation should never be employed. Small doses have no possibility of influencing the growth. Large doses are particularly objectionable because even though ineffective on the tumor, they cause grave sequelae in adjacent normal tissues.

PROGNOSIS

As we have previously noted, the clinical course of schwannomas is benign even though untreated. After complete surgical excision by enucleation, local recurrences do not take place. The well recognized tendency for neurofibromas, especially in von Recklinghausen's disease, to undergo sarcomatous changes is not a characteristic of schwannomas. In our series, 2 specimens (Cases 4 and 8) harbored areas which showed changes suggestive of malignant transformation (Fig. 5), but all the tumors were clinically and anatomically benign.

Various degrees of malignancy have been reported, though rarely, among schwannomas. Guleke's case, Lhermitte and Leroux's case, one of Stout's cases, and the first case of a series of 6 presented by Manteuffel-Szoelge appear to be authentic examples of either recurrent or locally infiltrating types of schwannomas. No instance of a genuine schwannoma that was capable of producing metastasis has been cited in the litera-

ture, with the possible exception of Case 4 in a series of peripheral nerve tumors reported by Cutler and Gross. Their patient had a huge tumor of the arm which showed some of the characteristics of schwannoma. The patient eventually died of pulmonary metastases.

END-RESULTS

One patient died 1 year after excision of a schwannoma of the neck following operation for repair of a hernia. The remaining patients are living (from 1 to 6 years following the date of admission) with no evidence of recurrence.

SUMMARY

Ten cases of schwannoma in the tissues about the head and neck are described and the first such tumors of the phrenic nerve are reported. In the light of recent evidence, an origin from the cells of Schwann appears to be the most acceptable. This tumor must be differentiated from the neurofibroma, as it is a specific tumor of the sheath of peripheral nerves and possesses distinct anatomic characteristics. In the neck, schwannoma must be differentiated from carotid body tumor in particular, and in the pharynx from lymphosarcomas. Aspiration biopsy permits accurate histological diagnosis. Schwannomas in the head and neck reported in this series were clinically and anatomically benign. They were radioresistant. None recurred following surgical excision.

NOTE.—Since the conclusion of this study 2 additional cases of schwannoma in the neck were encountered at the Memorial Hospital:

CASE 11.[1] F. A., white female, 33 years of age, was admitted to the hospital on November 1, 1942, for a painless swelling of the right neck of 14 months' duration. Examination revealed a soft, circumscribed, movable tumor, 3 centimeters in diameter, in the region of the carotid bulb. Aspiration biopsy was not done. At operation an encapsulated tumor was found beneath the internal jugular vein and common carotid artery. This tumor arose from the *phrenic nerve*, which had to be sacrificed.

CASE 12. M. C., white female, 39 years of age, was admitted to the hospital on December 5, 1942 for a painless mass in the right neck of 6 weeks' duration. Four years previously the right lobe of the thyroid gland had been removed at the Memorial Hospital because of an adenoma. Examination revealed a firm, movable, ovoid tumor, 1.5 centimeters in diameter, in the region of the carotid bulb. Aspiration biopsy was not done. At operation a spongy, encapsulated nodule was found to arise from the *vagus nerve*, which had to be severed to make possible removal of the tumor. So much of the vagus nerve had to be sacrificed that repair of the nerve was not feasible. The postoperative period was characterized by hoarseness, difficulty in swallowing liquids, and paralysis of the right vocal cord, but there has been a steady improvement of these symptoms.

[1]Reported by courtesy of Dr. George T. Pack.

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SULFADIAZINE TREATMENT OF BURNS

A Comparative Study

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THE successful reports regarding the use of sulfonamides locally in fresh wounds has stimulated certain workers to employ sulfadiazine as a spray in the treatment of burns. The excellent results of Pickrell have shown that sulfadiazine is similar to tannic acid in the treatment of burns with the added advantage of being bactericidal and producing an eschar which is flexible, transparent, and has less tendency to crack.

At the Cook County Hospital we have for years used, in the treatment of burns, various local therapeutic agents including tannic acid (℞ No. I), trinitrophenol solution (℞ No. II), gentian violet jelly (℞ No. III), ether soap (℞ No. IV), etc. In recent years, the Koch treatment has proved to be particularly advantageous. Although the results secured with these agents have been more or less favorable, it has always been our hope that new measures might tend to improve results. With our Nation at war, many burn casualties are to be expected, and therefore, particularly pertinent at this time is a study such as this; by making a comparative study of results obtained with the older measures and those obtained with the recently introduced sulfadiazine spray,[1] an attempt has been made to determine which is the best local therapeutic agent to use in treating burns.

In our study we divided the cases into 2 groups. In the first group we used sulfadiazine spray on the entire burned surfaces. In the second group of cases we subdivided the burned surfaces and used sulfadiazine spray on one-half of the burned area and nonadherent pressure dressings on the remaining half. We believed that by using the two methods of treatment in the same individual we would eliminate the personal factor of healing and, undoubtedly, would have a more accurate comparative study. The fact that each burned area was of the same degree, extent, and duration and that each area received the same preliminary cleansing with soap and water, allowed us to make definite deductions as to the advantages and disadvantages of each method.

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[1]Sulfadiazine (2 sulfanilamidopyrimidine) 3.0–3.5 per cent; triethanolamine, 8.0 per cent; sodium benzoate, 0.1 per cent; water sufficient to make 100 per cent.

PROCEDURE

On admission to the hospital, each patient with burns was rapidly examined and the cause of the burn, the length of time that had elapsed since injury, and the degree and extent of the burn were established. On a prepared chart, the extent and degree of the burn was indicated for future reference. On the back of these charts all other information was given.

Following recovery from primary shock, the local treatment of each patient consisted of careful aseptic soap and water cleansing[2] with débridement of the burn, under morphine sulfate sedation. The burn was then divided into approximately equal portions, in 5 instances, and half treated with sulfadiazine spray while the rest was treated with xeroform and pressure dressings. Sulfadiazine (3 per cent in triethanolamine) was sprayed onto the burned area with an atomizer (as suggested by Pickrell) every hour the first day, every 2 hours the second, every 3 hours the third and, if necessary, every 4 hours the fourth. During this time the burned area was protected by sterile sheets beneath a heat cradle. In most cases a satisfactory eschar was produced by the third day.

White soap, sterile water and cotton pledgets were used to cleanse the burn to prevent further damage to delicate surface cells.

When infection was absent, the eschar would loosen and separate spontaneously in almost 10 to 14 days. Saline compresses after 14 days would precipitate its separation. Sedation with morphine sulfate or phenobarbital was required in most cases to maintain comfort of patient.

Koch's nonadherent pressure dressing used on the remaining half of the burn consisted of the following layers: (1) 3 per cent xeroform in petrolatum base, impregnated in fine mesh gauze; (2)

[2]During this cleansing process, doctors scrubbed for 10 minutes and then wore caps, masks, and gowns and sterile gloves.

3 to 4 layers of sterile gauze; (3) large sterile cotton pad; (4) sterilized mechanics' waste or marine sponges for pressure; and (5) plain gauze or elastic bandage and splint in cases of extremity involvement. This dressing, like the sulfadiazine eschar, was not disturbed for 14 days unless evidences of infection were present (temperature, discharge, etc.).

General management. The general management of the patient varied according to the pathological physiology present. Particular attention was paid to primary shock, hemoconcentration, toxemia, and sepsis. Primary shock was combated with heat, rest, and morphine sedation in adequate dosage. General anesthesia or local burn therapy was considered contraindicated in the presence of primary shock.

Secondary shock or hemoconcentration was recognized by early and repeated hematocrit readings. Plasma was given early and in adequate amounts as recommended by Harkins (100 c.c. for every mm. rise above the normal reading—45).

The patient was placed on a high carbohydrate diet and fluid balance was maintained by intravenous fluid if necessary; 1,500 cubic centimeter urinary output a day has proved to be the best measure of fluid balance. Saline was given intravenously only if a blood deficiency was established by blood chloride determination.

Desoxycorticosterone acetate,[1] 1 cubic centimeter every 4 hours for 10 doses was given intramuscularly to all patients since recent workers have shown its value in decreasing plasma loss and minimizing hemoconcentration.

Toxemia was treated with the usual supportive measures, and we made sure that kidneys and liver functioned properly. We believed that since liver necrosis was a common finding in severe burns, oxygen to combat the stagnant anoxemia and glucose to maintain liver glycogen were undoubtedly of value. We, therefore, placed all severely burned patients on oral or intravenous glucose or both and nasal oxygen.

Sepsis, as evidenced by a spiking temperature and local infection and drainage, was controlled by hot wet dressings locally and, on one occasion, chemotherapy systemically. Caution must be used with sulfonamide therapy systemically when it is also used locally for fear of toxic absorption. Its use in septic burned patients with poor renal and liver function may also be detrimental, unless blood levels and toxic reactions are watched for carefully.

Although we are discussing only 10 burn cases, these represent a carefully selected and controlled group chosen from the many cases of burned patients admitted to the hospital. Hence, it is our opinion that a definite impression can be arrived at which might be of value to others in their choice of a local agent in the treatment of burns.

The following factors were used as a basis for the comparison of the two methods and for judging the efficacy of each and will be discussed individually: (1) ease of application, (2) toxicity, (3) incidence of infection, (4) degree of healing, (5) ease of removal.

To produce a sulfadiazine eschar, similar to one after the use of tannic acid, requires constant attention on the part of the nurse and attending staff since spraying must be frequent and thorough and aseptic precautions must prevail at all times. About one-fourth of our patients complained bitterly of a burning pain during each spraying episode. Xeroform-vaseline dressings, on the other hand, are painless, quickly and easily applied and require only one simple application, thus facilitating nursing care, as well as the patient's comfort. Pain was relieved in all cases by the xeroform-vaseline dressing because of its soothing property as well as the complete exclusion of air.

Although no patient developed any toxic reactions from sulfadiazine, we did note that rapid absorption of this agent from the burned area occurred. After 12 hours of spraying, one patient developed a blood level of 8.82 milligrams per cent of sulfadiazine. For this reason, we hesitated to use sulfadiazine over extensive areas for fear of toxic absorption. Xeroform dressings, on the other hand, were not associated with clinical evidence of toxicity. The fact that xeroform is recommended for internal use by *New and Non-Official Remedies*, 1940, is further evidence of its nontoxic properties.

Infection occurred in 23 per cent of the total area treated with sulfadiazine spray as compared to 7 per cent with xeroform dressings. Since each burn received the same preliminary cleansing with soap and water and since there were no marked differences in degree and duration, the only cause suggested for the greater incidence with the sulfadiazine method treatment is the time required for its application and the difficulty of maintaining asepsis during its administration. The accumulation of plasma (a good culture medium) beneath the eschar may also be a contributing factor to the greater incidence of infection. At each time of spraying with sulfadiazine, there is also present the possibility of a similar spraying of infection from the nose and throat of the nurse

[1] Percorten Ciba.

or doctor making the application, as well as from organisms normally present in air. Complete asepsis is extremely difficult to maintain throughout the 72 hours required for eschar formation, in spite of proper masking, sterile sheets, etc.

Xeroform pressure dressings, on the other hand, require only *one* application of an easily applied sterile dressing through which reinfection is difficult. This is strictly in accord with Orr's principles in the treatment of compound fractures; that is, decrease the incidence of reinfection by decreasing the frequency of dressings. Like Orr's treatment, Koch's principles apply to burn therapy—rest, pressure, and drainage.

A comparison of the degree of primary healing was very much in favor of the nonadherent pressure dressing type of treatment. The term nonadherent signifies that no superficial cells are damaged during the application of the dressing and also that the viability of the cells are unhindered during its removal, since nothing adheres to the dressing, nothing is pulled off. As a result, the incidence of healing (new skin formation in a second degree burn or clean granulation in third degree) with the nonadherent dressing was approximately 80 per cent whereas, with sulfadiazine, it was only 50 per cent. We believed that this was due to certain deficiencies of the eschar in the sulfadiazine type of treatment which holds true for any type of eschar producing agent. These deficiencies may be summarized as follows:

1. Eschars require time to cover completely the burned area; during this time reinfection occurs with resultant damage to the skin elements.

2. Eschars do some damage to the epithelial cells because of their property of protein coagulation as well as their tendency to adhere to the surface.

3. The accumulation of serum beneath the eschar forms a good culture medium in which organisms may grow.

4. This reinfection beneath the eschar may account for the transformation of some burns of second degree into those of third degree. The absence of pressure increases the plasma loss with its resultant hypoproteinemia, tissue edema, and poor healing.

5. Eschars have a tendency to crack or curl at the edges, thus leaving a portal of entry for infection.

The last comparison that was made was ease of removal of the various agents. Sulfadiazine proved to be difficult, painful, and tedious in its removal, while on the contrary xeroform was capable of being removed atraumatically, painlessly, and quickly.

SUMMARY AND CONCLUSIONS

A comparative study was made between sulfadiazine spray and nonadherent pressure dressing treatment of burns with the following results.

1. Although sulfadiazine presumably has the bactericidal properties of other sulfonamides, its application as a spray has all the disadvantages of other eschar forming agents, namely, reinfection frequently results, healing is incomplete, second degree burns may be transformed into those of third degree. It is more difficult and painful to apply and more difficult to remove than the nonadherent pressure dressing.

2. This study served to demonstrate again the advantages of nonadherent pressure dressing as compared to the eschar type of burn treatment because its application, as well as its removal, is easy, quick, and painless. It required less nursing care, showed lower incidence of infection, greater degree of healing, no evidence of toxic absorption, affords greater comfort to the patient. In addition it is a good preliminary treatment in cases of deep burns in which grafting is necessary since a minimum of time is necessary before grafting can be done. No time is lost in grafting because the use of pressure and the fine mesh gauze result in a good bed for the graft.

3. The combination of a chemotherapeutic agent applied as a nonadherent pressure dressing might be the procedure of choice because it would have not only the bactericidal effect of the sulfonamide but as well all the advantages of a nonadherent pressure type of dressing.

4. Regardless of the local treatment, the surgical principles so frequently advocated by Koch must be applied if successful burn treatment is to be expected; namely, convert all burns from contaminated wounds to clean wounds by aseptic and atraumatic cleansing with soap and water. Second, close the clean wounds and keep them closed and clean until healing occurs.

5. Our discussion of the local treatment of burns should not mask the importance of proper general management of primary shock, hemoconcentration, toxemia, and sepsis.

Shortly after completion of this study, we read the paper by M. Rothman and associates, on the treatment of burns with 2.5 per cent sulfadiazine in 8 per cent triethanolamine solution. Possibly in a larger series of cases our results with sulfadiazine spray would have been more favorable.

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A NEW NEEDLE FOR THE TREATMENT OF SHOCK BY STERNAL INFUSION

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COMBATING shock is a major problem facing medical officers in the field of battle. Whether the shock is due to trauma of gunshot, shrapnel, or bayonet wounds, concussion, burns, or hemorrhage, early treatment and breaking up of the "Cycle of Death" as described by Moon, is of extreme importance. The introduction of plasma or the albumin fraction of plasma into the circulation, and the use of oxygen and adrenal cortex extract are the most effective means of meeting the problem that have been discovered to date.

The work of Kendrick and Newhouser in making plasma prepared from blood donated through the American Red Cross available for use in the field of operations, has undoubtedly saved many lives by preventing shock from progressing to an irreversible stage in many of the battle casualties. The standard Army-Navy package of dried human plasma is now packaged with water, tubing, and needles necessary for restoring it, and administering it intravenously.

Because of the underlying pathological changes that take place in shock, it is of the utmost importance that the fluid used in combating it be given into the circulatory system. The increased endothelial permeability, which is part of the picture, has caused loss of fluids into the tissues outside of the vessels, with consequent hemoconcentration, reduced blood volume, and reduced volume flow, and plasma or albumin solutions given outside the vascular system cannot be expected to help. The collapse of peripheral vessels, and the stagnation of blood flow in the veins make the intravenous administration of fluids difficult and practically impossible at times when the need is most urgent. Tocantins, O'Neill, and Price have shown the feasibility of injection into the marrow cavity in order to reach the general circulation in these cases, and, in adults, the sternum has been selected as the site of choice.

The advantages of reaching the circulation by this route are many. The sternum is easily punctured with a properly designed needle. Once the needle is in place there is no doubt of the fact that the fluid is entering the circulatory system. Movements by, and of, the patient do not dislodge the needle easily, as is often the case when it is in a thin walled arm vein. Also, concentrated plasma or albumin can be injected forcibly, with no fear of rupturing the vein and wasting the material in surrounding tissues. Faxon and Churchill, in describing the treatment of the burns resulting from the Cocoanut Grove fire in Boston, mention the difficulty encountered in giving intravenous plasma, and deplore the fact that materials for intrasternal administration were not at hand. Chilcott at St. Francis hospital in Evanston, Illinois, being unable to keep a needle in the vein of a severely burned patient, gave 12 units of plasma through one sternal puncture, with recovery.

After over 1700 diagnostic sternal punctures done at the University of Illinois, College of Medicine, and the Cook County hospital in Chicago, and after talking to Lieutenant Colonel Douglas B. Kendrick, Jr., at the Army Medical Center in Washington, D. C., and using the needles available for the purpose there, the writer designed a needle which he believes is better and more easily used for sternal puncture and fluid administration than is any other available at present (Figs. 1 and 2).

This needle is simple and can be made cheaply in large numbers for inclusion in plasma and albumin packages for use by the Army and Navy in combat and other zones. The flange on the hub makes it easier to apply the pressure necessary to penetrate the anterior plate of the sternum and also prevents slipping of the fingers and possible contamination of the point of the needle. The knurling of the hub permits easy rotation of the needle in penetrating the bone. The simple lock which holds the stylet in place prevents its displacement and blocking of the needle by a particle of bone.

The following technique may be used in administering fluids intrasternally. The plasma, albumin, blood, or other fluids are made ready to be given. The site for administration, usually the manubrium or the body of the sternum opposite the 2d or 3d interspace, is chosen, and the overlying skin is cleaned with iodine and alcohol or an acetone-alcohol-mercurial mixture. The skin and underlying tissues down to the sternum are

From the 27th Evacuation Hospital.

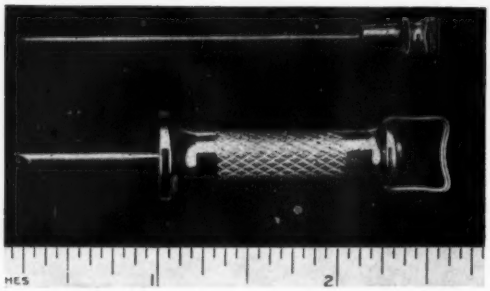

Fig. 1. Photograph of needle for administering plasma and fluid.

anesthetized with procaine. The needle is inserted through the skin down to the bone in the midline. Then, with the point toward the head, and at an angle of about 45 degrees with the sternum, the needle is forced into the marrow cavity with pressure and a rotary, boring motion. The entrance into the cavity is usually indicated by a distinct lessening of resistance as the anterior plate of the sternum is penetrated. Then, to check the presence of the needle point in the marrow cavity, and possibly to open up sinusoids and allow more rapid flow of fluids, the stylet is removed, and rapid aspiration with a 5 or 10 cubic centimeter syringe is attempted. When the needle is in place in the cavity, there will be a gush of blood and marrow into the syringe, and from 1 to 2 cubic centimeters should be withdrawn. Following this the fluid can be administered either by drip, or, if speed is urgent, by forcible syringe injection. Because of the coagulability of marrow, if there is any delay between the above aspiration and fluid administration, the stylet should be replaced to prevent clotting in the needle, and occasionally it may be necessary to inject about 20 cubic

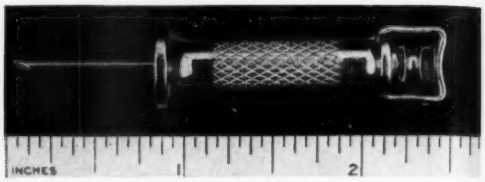

Fig. 2. Needle assembled. Note flange on hub and knurling.

centimeters of physiological saline by syringe to start the flow when the drip method is used. When large quantities of fluids are given over a long period of time, it is well to remember that the velocity of flow sometimes tends to increase with time, and that this increase should be controlled to prevent circulatory embarrassment.

Using the above method with the needle suggested, medical officers of the Post Hospital and the 27th Evacuation Hospital at Camp Breckinridge, Kentucky, with no previous experience with sternal punctures, have had no difficulty with the administration of fluids.

Because of the ease with which it can be used and manufactured, it is believed that the needle described for use in the intrasternal administration of fluids would be a valuable aid in the treatment of shock in the combat zone and certain civilian emergencies.

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A STUDY OF EXTRACELLULAR WATER CHANGES IN PREGNANCY

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STANDER and Pastore write "The weight gain during pregnancy is out of proportion to the weight of the products of conception, which approximately account for one-third of the total gain. This excess is undoubtedly mainly due to fluid retention not only in the circulation but also in the tissues. This would indicate that approximately 16 per cent weight increase over the nonpregnant weight is due to fluid. Experiments have already shown that there is about 20 per cent dilution of blood due to hydremia, and it is reasonable to assume that there is an equivalent dilution of the tissue fluids." Observations consonant with this supposition are (a) the marked postpartum diuresis, (b) the simultaneous rapid weight loss in the early puerperium, and (c) the atonic and flaccid condition of the tissues after the diuresis (discharge of edema water).

Beck, on the other hand, writes that practically all of the weight gain, over and above that represented in the conception product is to be accounted for by maternal fat.

The water retention of pregnancy has not been investigated extensively, except for studies of blood dilution and of blood volume increase. Analyses of weight gain in pregnancy are obviously nonspecific.

Unfortunately, there is not available a method for the measurement of total body water. However, there are means of determining the *extracellular* water, at least roughly. It is uncertain whether the water increase in normal pregnancy is confined to the extracellular space. *Extracellular* water, however, does make up at least ⅓ of the total body water, and even occult edema frequently shows up as a marked increase in this extracellular water. Measurements of extracellular water, then, show promise of yielding some information about water retention in pregnancy.

In the present paper are reported the results of repeated measurements of the thiocyanate-available water (roughly equivalent to extracellular water) in a large series of patients. Changes in available water are correlated with weight changes, and an attempt is made to account for the increments in and disposition of the water.

From the Margaret Hague Maternity Hospital.

MATERIAL AND METHODS

The total number of patients studied was 442. These were in 2 groups.

1. Sixty-seven patients were taken at random from the antepartum clinic, the only selection being for patients early in pregnancy who were distributed over a wide range of body weights. Measurements of thiocyanate available water were made on the day of selection and were repeated at 32 to 35 weeks of pregnancy. In a few cases third measurements were made antepartum.

2. For a time, all clinic patients were routinely given the test at the 31st to 33d week, and repeated at the 35th to 37th week of pregnancy. These patients, totaling 375, are included in the present study. A few of these had third tests at term.

The patients were given 1000 milligrams of sodium thiocyanate by mouth and were instructed to save all urine until the following morning (average 21 hours later) when the urine collection was completed and a blood sample was taken. The urinary loss of thiocyanate was measured.

Thiocyanate was determined in duplicate in serum and urine by a method described elsewhere (Chesley). Completeness of urine collection was checked by measurement of the creatinine excretion, by the method of Folin (Peters and Van Slyke). When considerable volumes of urine obviously had been lost, the test was discarded.

The thiocyanate available water was calculated by dividing the serum concentration of thiocyanate into the amount of thiocyanate left in the body (i.e. 1000 mgm.—urinary excretion). The quotient thus obtained represents the volume of water in which the thiocyanate is distributed. With minor reservations, the water so measured is extracellular (Chesley and Chesley, 1941).

RESULTS

Available water gain up to 34th week of gestation. At the time of the first measurement of available water, 10 patients were in the first trimester of pregnancy and 57 were in the second. Of these latter, 40 were less than 20 weeks pregnant. The average time in pregnancy at which the test was first done in these 67 patients was 18 weeks. In all cases, the test was repeated at the 32d to 36th

(average 34th) week. Over this interval of 16 weeks (average) the mean rate of available water gain was 208 milliliters per week. In the 10 patients first done at 11¼ weeks (average), the mean rate of water gain over a 22 week period was 201 milliliters per week.

We (6, 7) have previously found that about 1/5 of patients in the last 6 weeks of pregnancy will have abnormally high values for available water, i.e. edema—frank or occult—is present. Such patients may be considered to have gained more than the normal amount of available water because: (1) their volumes of available water are considerably greater than the average normal; (2) they very frequently show edema; (3) a high proportion develop the pre-eclamptic syndrome; and (4) they show an unusually large loss of available water in the first 6 days postpartum.

Of the 67 patients studied 14, or 20.9 per cent, had gained so much water between the first and second tests as to fall into the abnormal range. Of these 14 cases, 8 developed pre-eclampsia. We shall consider these 14 cases separately and shall regard the remaining 53 patients as having gained normal amounts of available water. For these normal patients the average rate of gain in available water was 157 milliliters per week. Six showed a gain of 0 to 50 milliliters; 5 a gain of 51 to 100 milliliters; 16, of 101 to 150 milliliters; 12, of 151 to 200 milliliters; 9, of 201 to 250 milliliters; 3, of 251 to 300 milliliters; and 2, of 301 and more milliliters. The mean was 157 milliliters; standard deviation, 75 milliliters; mode, 136.3 milliliters; median, 150 milliliters.

It would seem reasonable to suppose that the rate of water retention accelerates as pregnancy progresses. In order to determine whether this occurs, the data for the 53 normal patients have been further analyzed: (1) In the 7 patients first measured at about 11 weeks the average rate of water gain is 134 milliliters per week, perhaps indicating a slightly lower rate of gain in the earlier weeks of pregnancy. (2) When the second measurement of available water was made at or before the 33d week, the average gain was 145 milliliters per week. In patients whose second measurement was made at 34, 35, or 36 weeks, the average gain was 164 milliliters. This might point to an increasing rate of water gain in these later weeks. While these differences *in rate* of gain seem slight, it must be remembered that they are minimized by the long interval between tests (average 16 weeks.) The differences in *total* water gained are quite definite.

Comparing the weight gain with the water gain in the 53 normal patients, we find that the average weight gain was 6.67 kilograms, with an average available water gain of 2.51 kilograms. Thus the available water added accounts for 38 per cent of the weight increment.

In the 14 patients who had abnormally high proportions of available water in the second test at the 32d to 36th week, the average rate of gain in water was 402 milliliters per week—two and a half times that in the normal patients. The average weight gain was 8.17 kilograms, and the available water added made up 77 per cent of the weight increment.

If we assume that the average normal rate of available water gain is about 150 milliliters per week for the first 34 weeks, then at the end of that time the total increment would be 5,100 milliliters. With certain reasonable assumptions as to the status at 34 weeks, this can be accounted for as follows: (1) The fetus weighs about 2000 grams (Stander), and if its available water be 30 per cent, 600 milliliters of the water measured is in the fetus. (2) The amniotic fluid would amount to about 1200 milliliters (Beck). If half of this be included in the measurement of available water (Chesley and Boog), then another 600 milliliters would be accounted for. (3) The uterus may have gained as much as 1000 grams (assumed from uterine weights given by Reynolds). Perhaps as much as 300 milliliters of available water would be found here. (4) The increase in blood volume occurring during pregnancy, reaches its maximum at about the 34th week. Taking the data of Thomson and associates which show a gain of 20 milliliters of blood per kilogram of weight, and applying them to a 60 kilogram patient who gains 6 kilograms up to this time, the increase in blood volume would be 1740 milliliters; using the 82.7 per cent water content of blood in late pregnancy as found by Oberst and Plass, this volume of blood would contain 1440 milliliters of water which is included in the measurement of available water. (5) Finally, Goudsmit and Louis have found that a decrease in serum proteins of 1 gram per 100 milliliters will result in an increase in available water amounting to 3.8 ± 0.8 per cent of the body weight. Many writers have found that in pregnancy the serum proteins do decrease by just about 1 gram per 100 milliliters (Stander). In a 66 kilogram patient, this factor might then account for an available water increment of about 2500 milliliters. These expected increments total 5,140 milliliters, as compared with the volume of 5,100 milliliters obtained by calculation from the average measured rate of gain.

Available water gain after the 32d week. Since the volume of available water in late pregnancy

TABLE I.—THE DISTRIBUTION OF RATES OF LOSS AND GAIN IN AVAILABLE WATER IN LATE PREGNANCY

Rate of change in water—ml. per wk.	Cases
Loss	
301+	9
201–300	7
101–200	19
0–100	27
Gain	
0–100	34
101–200	56
201–300	58
301–400	62
401–500	43
501–600	20
601–700	17
701–800	9
801–900	4
901+	10

Mean: 263 ml. Standard deviation: 316 ml. Mode:* 267 ml. Median: 260 ml.
*The three groups between 100 and 400 ml. were combined for this calculation, since the numbers of cases in each group were nearly the same.

can be greatly modified by the limitation of dietary salt (Chesley and Annitto), only those patients on unrestricted diets will be presented as "normals." This may be further justified by the fact that when such salt restriction was imposed, it was usually because of clinical signs pointing to the possible development of toxemia. An additional 55 patients are not included because their proportions of available water were abnormally high.

In 375 normal patients selected as here indicated, the rate of gain in available water after the 32d week averaged 263 milliliters per week although there was a very wide variation and some patients actually lost water (Table I). This average rate of water gain is almost twice that described for the preceding weeks of pregnancy.

This is of particular interest since at this time (32d week) the blood volume nearly reaches its maximum and shortly thereafter begins to diminish (Thomson et al.). Also the serum proteins have passed their minimum point, and the amniotic fluid volume is decreasing (Beck). These factors, which seem to bulk so large in explaining water retention up to this period in pregnancy, would no longer seem to operate in further water retention. After the 32d week the fetus approximately doubles in weight (Stander); thus not much more than 600 milliliters of the added available water is to be found here. Presumably the rest of the water gained contributes to the extracellular hydration of the maternal tissues.

From the data in Table II it appears that the average rate of water gain diminishes somewhat

TABLE II.—THE AVERAGE RATE OF GAIN IN AVAILABLE WATER IN THE LAST WEEKS OF PREGNANCY

Time of second test	34 or 35 weeks	36 or 37 weeks	38 or 39 weeks	40 or more weeks
Cases	80	217	65	9
Time of first test—wks.	Average gain in available water in milliliters per week			
30	341	244		
31 or 32	315	277	202	
33 or 34		313	213	107
35 or 36			210	240

in the last 3 or 4 weeks of pregnancy. Of the 56 patients whose available water was measured after the 34th week, and remeasured in the 38th week or later, 16, or 28.6 per cent, lost water between tests. Perhaps this loss of water is correlated with the well known weight loss which often occurs as labor impends.

Since Stander and Pastore suggested that the water gain in pregnancy should total about 16 per cent of the nonpregnant weight, it is interesting to note that the rate of gain in absolute amounts of available water seems to bear no relation to the body weight (Table III). In this connection, Bray found that the body build did not influence the weight gain, although this has not been uniformly the finding of other writers (see Bray for review).

An approximate estimation of the total gain in available water in pregnancy may be made. It has been calculated here that the gain up to the 34th week might be about 5,100 milliliters. The average gain after this time is about 210 milliliters per week (average of the four lower right boxes in Table III). Thus the total water gain would be about 6,300 milliliters. Of this perhaps 1500 to 2000 milliliters, as measured, are to be found in the fetus, placenta, and amniotic fluid, leaving 4,300 to 4,800 milliliters for hydration of the maternal tissues. Roughly, this would represent an average of 9 to 10½ pounds of the mother's

TABLE III.—THE AVERAGE RATE OF GAIN OF AVAILABLE WATER IN LATE PREGNANCY, DISTRIBUTED BY WEIGHT GROUPS

Body weight in pounds	Less than 120	121–140	141–160	161–200	More than 201
Cases	21	117	140	86	11
Average gain per week in ml.	321	249	275	241	311
Proportion of patients losing water, %	9.5	18.8	15.0	19.8	0.0

weight gain. Some of this may be lost in the prelabor weight loss.

Relation of water gain to weight gain in late pregnancy. We have shown in a previous paper (7) that there is very little correlation between the gain in available water and the weight increment, especially in the last 10 weeks of pregnancy. In half of the patients studied, the weight of available water added was greater than the increase in body weight; in 9 per cent of all cases the patients *lost weight* while *gaining available water*. This might be explained in 2 ways: (1) Possibly the permeability of certain cells increases as pregnancy progresses, so as to admit the thiocyanate thus giving an apparent increase in extracellular water. (2) There may be a shift of intracellular water out into the extracellular space. Such a shift is believed to occur in toxemia (McPhail), and may occur toward the end of normal pregnancy.

SUMMARY AND CONCLUSIONS

Repeated measurements of thiocyanate-available water (roughly, extracellular water) were made in 442 patients at different times in pregnancy ranging from the 8th to 40th week.

There seemed to be a gradually accelerating rate of gain in available water.

The total gain in available water up to the 34th week of gestation averaged about 5 liters. This can be accounted for on the basis of certain factors known to be operative in normal pregnancy.

After the 32d week, there was a greatly increased average rate of available water gain. Practically all of this seemed to represent hydration of the maternal tissues. Such water gain occurred despite the fact that certain factors operative in earlier pregnancy now seemed opposed to further water retention.

In the last weeks of pregnancy, many patients lost water. This loss may be correlated with the well known weight loss often occurring just before delivery.

The total gain in available water was calculated to average about 6.3 liters, of which 1.5 to 2.0 liters, as measured, are to be found in the conception product.

Hydration of the maternal tissues apparently occurred. The average weight of water thus represented was 9 to 10½ pounds. Some of this may be lost with the prelabor weight loss.

There is not a close correlation between weight gain and available water gain in late pregnancy. In half the cases, the weight of water gained was greater than the weight increment.

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INTERNAL FIXATION IN INJURIES OF THE ANKLE

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AMONG the injuries of the ankle, which are becoming more common as a result of the general speeding up of heavy industry and the popularity of winter sports, is the serious complicated fracture or dislocation that presents a problem in treatment. In these cases the ideal conservative methods fail, not only because it is usually impossible to effect an accurate reduction by manipulation, but because there is no adequate means of external fixation. These injuries, then, fall necessarily into an operative group, requiring open reduction and some form of internal fixation to maintain the corrected position. It is the purpose of this paper to classify those injuries that are operative and to describe methods of reduction and fixation that have proved to be successful. Such operative treatment should be undertaken by only the highly qualified surgeon.

Operative reduction, when indicated, should be carried out as soon as possible, preferably within from 24 to 48 hours after the injury. In the interval, in order to prevent swelling and the formation of blebs, the ankle is kept bandaged, elevated, and immobilized by means of a molded posterior splint of plaster.

FRACTURE OF THE LOWER END OF THE FIBULA

The lower fibula may be fractured as the result of forcible external rotation of the foot or of turning the foot directly outward on the leg. The astragalus as it twists in the joint mortise and strikes against the edge of the external malleolus is the shearing force that causes the fracture. Such a fracture is the typical injury received in skiing when the point of the ski, turned outward, catches in the snow, and the skier pitches forward, twisting the ankle.

The fracture line is usually oblique from side to side, either running from a point slightly above the top of the astragalus upward and backward for a distance of about 2 inches, or extending as a long fracture line with its center at the joint surface. Operative indications should be recognized in fractures of the lower end of the fibula under the following circumstances: (1) in the short oblique fracture when the fibular end is displaced outward and backward with accompanying widening of the joint mortise; (2) in the long oblique fracture in which the tibiofibular ligamentous structure is damaged, and the fibular fragment rotated backward and outward with accompanying widening of the joint mortise (Figs. 1 and 2); (3) in fractures with irregular serrations of the fragments that preclude alinement by manipulative measures (Fig. 3). (An attempt at closed reduction may be made after the ankle has been prepared for operative interference, but it is seldom successful.)

Technique of operation. An incision is made over the fracture directly in the long axis of the fibula. The fracture cavity is cleaned out. The fracture is reduced, the amount of force necessary to effect reduction being much greater than the size of the fragment and the degree of the displacement would seem to require. A long vitallium screw is introduced through the cortices of the fibula and tibia, the exact direction of the screw depending on whether the outward or the rotary displacement is the offending factor (Figs. 4 and 5). A plaster boot is applied with the foot straight and at the right angle to the leg.

TRIMALLEOLAR FRACTURES

The trimalleolar fracture, consisting of fractures of the posterior tibial surface and both malleoli, presents no problem when the triangular-shaped fragment of the tibia is small in size. On the other hand, when a large fragment is separated which, in turn, disrupts the gliding weight-bearing surface of the tibia, it is difficult to reduce the fracture and to maintain the fragment in the corrected position. The poor end-results in this type of fracture are well known (Fig. 6). Disability is particularly marked in women, who are most likely to sustain this fracture, because of the fact that when high heels are worn the weight-bearing line falls through the posterior half of the tibial surface.

Operative reduction with internal fixation is indicated when the posterior tibial fragment includes a quarter or more of the tibial surface. A method that is applicable to fresh trimalleolar fractures is the following:

Under fluoroscopic control and with verification of the position by "spot films," a long, sharply pointed and beveled Steinmann pin is driven into the posterior tibial fragment, to the outer side of

Fig. 1. Fig. 2. Fig. 3.

Fig. 1. A fresh fracture of the long oblique type showing the fragment displaced outward and rotated, and the joint mortise widened.

Fig. 2. An unreduced oblique fracture of the fibular end, 15 years after the injury, showing the permanently widened joint mortise. Patient still complains of weakness and pain in the ankle.

Fig. 3. Fracture of the lower end of the fibula with irregular serrations that preclude reduction by manipulation.

the tendo achillis. The pin is inserted at a slightly upward angle to avoid its slipping when pressure is applied in reducing the fragment. Reduction is accomplished, and the fragment held in position by means of the pin.

A short incision is made on the anterior surface of the tibia, internal to the anterior tibial tendon and at the best level for the insertion of a screw. Small drill holes are made through the lower tibial shaft and the posterior fragment, the tibia being drilled first at a point determined by the size of the fragment. If there is any question as to whether the fragment has been drilled properly, fluoroscopic visualization in two diameters is advisable. A screw is then introduced. In order to permit close approximation of the posterior fragment, the screw used should be one shouldered near the head, or the drill hole in the anterior cortex should be enlarged to permit setting the screw. As the screw is being tightened, care must be taken to note when the reduction is complete; otherwise there is a danger of stripping the bony threads by continuing the tightening process.

The fracture is then treated as one of the Pott's type, and, if possible, reduction is accomplished by the routine manipulative method. When the fracture is of the irreducible type, the anterior tibial incision is enlarged, and the reduction is

Fig. 4. Reduction of the long oblique fracture shown in Figure 1.

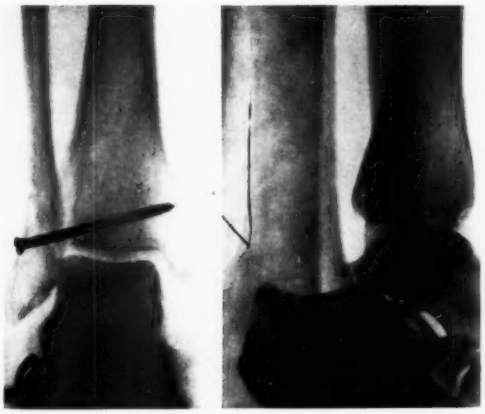


Fig. 5. Reduction of the fracture with irregular serrations shown in Figure 3.

completed according to the technique that is described under the section on Pott's fracture.

A molded plaster shell, or a circular cast, is applied with the foot in the position of inversion and at the right angle to the leg (Fig. 7, a, b, c, and d).

FRACTURE OF THE ANTERIOR TIBIAL SURFACE

A fracture of the anterior weight-bearing surface of the tibia similar to that of the posterior surface, in which a wedge-shaped fragment is broken off and the foot displaced forward, requires operative reduction. Particular care must be taken in handling this fracture, which is practically always of the comminuted type (Fig. 8, a and b).

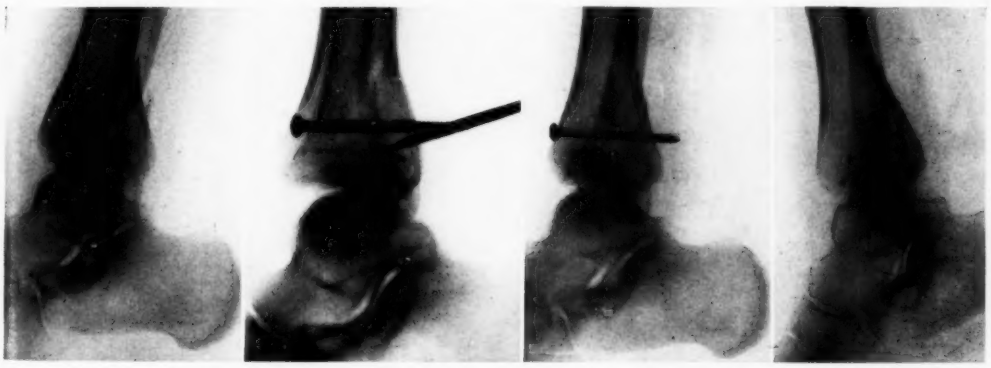
Technique of operation. An incision of sufficient length to provide ample exposure for inspection is made on the anterior surface of the tibia, internal to the anterior tibial tendon. A long pointed Steinmann pin is driven into the anterior fragment, by means of which it is manipulated into position and maintained while drill holes are being made. A small drill hole is first made through the fragment, its site being determined by the size and displacement of the fragment, and then a drill hole is made through the lower tibial shaft. A screw is inserted and tightened. A plaster boot is applied in either one or two sections, depending on the amount of swelling that may be expected. If the comminution is extensive, the foot should be immobilized in the position of slight toe-drop in order that the weight-bearing line will lie backward and thus facilitate early use.

FRACTURE OF THE INTERNAL MALLEOLUS

Occasionally in an isolated fracture at the base of the internal malleolus, an obstacle to closed reduction is presented by a curtain of soft tissue that is interposed between the tibia and the fractured malleolar surface (Fig. 9). If such a fracture is not accurately reduced, a fibrous union takes place, causing the area to be tender and painful and the joint mortise to be unstable.

Operative interference is required to release the fragment from the tight offending curtain of periosteum and the ligamentous band. Once the fragment has been freed, it is surprising with what ease the reduction is accomplished and the

Fig. 6. A typical poor end-result from conservative treatment of a trimalleolar fracture, showing displacement of the posterior fragment and arthritic changes.



a b c d

Fig. 7. Roentgenograms showing: a, a fresh trimalleolar fracture; b, the Steinmann pin and screw in place; c, the screw alone in position; d, the end-result 7 months after reduction.

Fig. 8. a, left, Comminuted fracture of the anterior tibial surface with forward displacement of the foot; b, reduction and fixation of the fragment by a screw.

Fig. 9. A fracture of the internal malleolus irreducible by manipulative measures because of interposed soft tissue.

corrected position maintained. Following the reduction, the malleolar fragment is fixed to the tibia by means of a chromic catgut suture, which is first carried around the fragment and then passed through a drill hole in the tibia. A plaster boot is applied with the foot in the position of slight varus and at the right angle to the leg.

POTT'S FRACTURE

One obstacle to the reduction of a Pott's fracture by the routine manipulative method is the interposition of a curtain of soft tissue between the inner malleolar fragment and the tibia. This complication has just been discussed.

Another obstacle to reduction is the dislocated posterior tibial tendon (Figs. 10, a and b and 11). A Pott's fracture that is complicated by this dislocation may be treated as follows:

An incision is made below the inner malleolus. The tibialis posticus tendon is released from between the articular surfaces of the astragalus and the tibia, and the displaced astragalus is restored

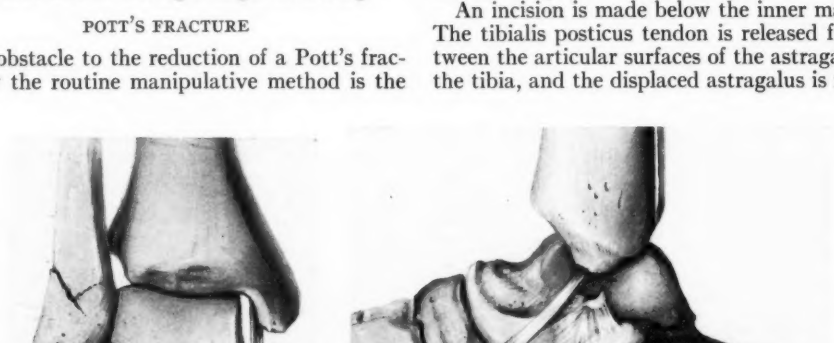


Fig. 10. a, left, Displacement of the posterior tibial tendon under the internal malleolus. Note the widening of the joint mortise. b, Lateral view of the displaced posterior tibial tendon.

Fig. 11. An irreducible Pott's fracture due to displacement of the posterior tibial tendon.

to its normal position. Torn ligaments are carefully repaired to prevent a recurrent dislocation of the tendon. Following the reduction, a posterior plaster slab and a pressure bandage are applied to hold the foot in the position of slight equinovarus.

SEPARATION OF THE TIBIA AND FIBULA

A separation of the tibia and fibula as the result of the tearing of the tibiofibular ligament may occur in conjunction with a fracture in the region of the ankle or as a separate entity. The recognition and treatment of this lesion are important, because of the disability that may ensue from the disrupted relation between the astragalus and the tibia by the widening of the ankle mortise.

Internal fixation is the best form of treatment. A Kirschner wire, cut with threads, is drilled through the tibia and fibula, as near to the joint as possible. The holes in the skin are enlarged to permit the insertion of two ferrules equipped with thumb nuts for tightening (Fig. 12). If traction is needed in managing an accompanying fracture, a Braun splint is used, with the ends of the wire serving as attachments for the traction (Fig. 13, a and b). The traction splint remains on until union is sufficiently solid to permit the removal of internal fixation and the application of a plaster boot.

SEPARATION OF THE LOWER EPIPHYSIS OF THE FIBULA

In this epiphyseal injury, the fragment is rotated backward, with the tip of the fibula acting as a fulcrum, and it occasionally takes with it a jagged spicule of bone from the fibular shaft. Reduction by closed methods is prevented both by the fulcral end of fibula and spicule of bone.

Fig. 12. Separation of the tibia and fibula, before and after reduction.

The displacement is easily corrected after operative exposure of the fracture. A chromic catgut suture is used to hold the fragment in position. The ankle is immobilized in a plaster cast with the foot turned a shade inward. Care must be taken not to tilt the fragment outward at the epiphyseal line by inverting the foot too much (Fig. 14, a and b).

RECURRENT DISLOCATION OF THE PERONEAL TENDONS

Recurrent slipping of a peroneal tendon over the lower end of the fibula is accompanied by an uncomfortable jarring snap from which the patient seeks relief. The underlying pathology in these cases may be lax ligaments, a shallow groove for the tendon, or the presence of a supernumerary tendon that lies farther out beneath the tip of the malleolus than do the other tendons.

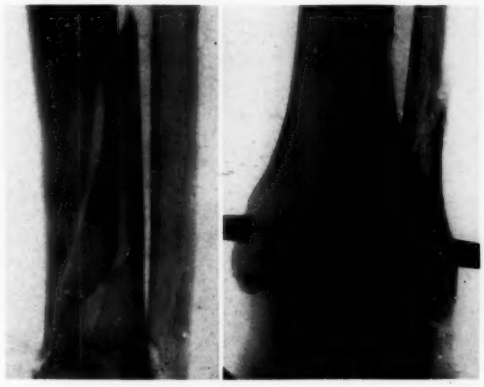


Fig. 13. a, left, Separation of the tibia and fibula associated with comminuted fractures of the tibia and fibula, before reduction. b, After reduction.

a a b

Fig. 14. a, Separation of the lower epiphysis of the fibula, showing backward rotation of the fragment including a spicule of bone from the fibular shaft, and forward displacement of the foot. The contour of the epiphyseal line prevents reduction. b, End-result showing a practically normal joint.

Operative repair is indicated in recurrent dislocations. In a case in which a supernumerary peroneal tendon was found to be dislocated, the following technique was carried out:

An incision was made in the direction of the long axis of the peroneus longus. The superior retinaculum was found to be rudimentary, narrow, thin, and ruptured at its attachment to the fibula. An accessory peroneal tendon, comparable in size to the peroneus longus, was lying in a shallow groove near the tip of the fibula. To prevent recurrence of the dislocation, this accessory tendon was first attached to the master tendon both above and below the malleolus. The retinaculum was repaired and reinforced by a slip of the cruciate crural ligament. A plaster boot was applied with the foot at the right angle to the leg and in slight varus (Fig. 15).

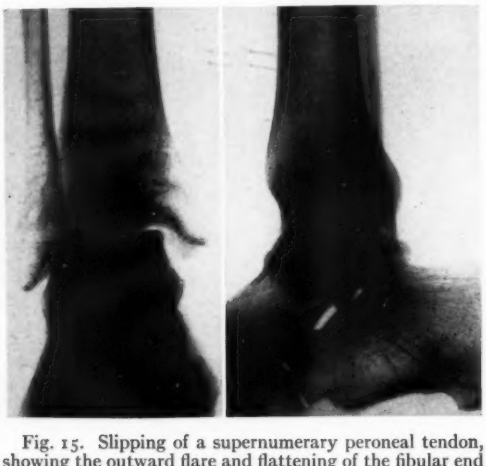


Fig. 15. Slipping of a supernumerary peroneal tendon, showing the outward flare and flattening of the fibular end due to pressure of the displaced tendon.

The patient was able to resume skiing in the following winter.

AFTER-CARE

The secure fixation of the fragments ensured under operative management makes it possible for use to be resumed early, thereby materially shortening the convalescent period. Weight-bearing is a far more satisfactory means of promoting the return of function than the application of heat and massage, although in the presence of contraindications to weight-bearing, physiotherapeutic measures may be used.

As soon as the wound has healed, and while the foot is still in the protective dressing, the patient may begin to bear weight with the aid of crutches. Full weight-bearing may be resumed in about 4 weeks following recurrent dislocation of the peroneal tendon, or fractures of the internal malleolus or the lower end of the fibula. In the other types of injuries, full weight-bearing is possible at about the 6th week after the injury. If the fractures have been comminuted, full weight-bearing should not be attempted for from 6 to 8 weeks.

The screw should be removed in all cases after union is complete. Local anesthesia may be used in this procedure.

SUMMARY

The accurate reduction that is essential to the successful treatment of injuries around the ankle cannot be obtained by conservative methods in certain complicated fractures and dislocations. These cases fall necessarily into a group that requires not only open reduction, but also some form of internal fixation. It is important that

operative indications are recognized promptly and that manipulative treatment is avoided.

A classification of those injuries that require operative treatment has been presented, and methods that have given excellent results have been described.

THE ELECTROENCEPHALOGRAMS OF MONKEYS FOLLOWING THE APPLICATION OF MICROCRYSTALLINE SULFONAMIDES TO THE BRAIN

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THE sulfonamides have been proved to have a direct antibacterial action when applied to contaminated and infected wounds in general, and should be of similar value in wounds of the brain if undesirable side effects do not contraindicate their use.

A number of histological studies (2, 4, 5, 6, 10, 12, 13) have been reported which show that the crystalline compounds placed on the brain or in brain wounds acted as foreign bodies, caused inflammatory reactions, became encysted, but finally disappeared completely. Nerve cells, myelin sheaths and neuroglia, adjacent to the compounds, showed no changes. The inflammatory reactions produced remained as local ones and lasted only as long as the drugs remained. The intensity and duration of the reactions about the compounds varied only with the amounts applied and the solubility, which influences the rate of disappearance and therefore the duration of the reaction. In treated wounds the late end scarring was no more intense than in comparable wounds in which no drug had been implanted. From the histological studies alone it seemed that the use of sulfonamides in potentially infected or infected wounds of the brain was justifiable, in spite of the transitory reactions, if they were used in moderation.

The first communications suggesting that more circumspection was necessary than the histological studies had demanded, appeared in 1942. Watt and Alexander reported 5 patients who had epileptic seizures following the application of sulfathiazole to the brain. Pilcher, Angelucci and Meacham pointed out the epileptogenic properties of sulfathiazole when applied to the brain of animals and warned against its use. Naffziger had 1 patient who developed status epilepticus following its use on the brain.

In 1940, Professor Adrian stated that he had carried out electroencephalographic studies on anesthetized rabbits after sulfanilamide and sulfapyridine had been applied to the brain. He found little effect on the electrical activity of the cortex after sulfapyridine and slight depression after sulfanilamide. At this time he had not done experiments with sulfathiazole, and sulfadiazine was not yet available.

The purpose of this communication is to report the effect of the application of sulfanilamide, sulfapyridine, sulfadiazine, and sulfathiazole on the electrical activity of the brain of the unanesthetized monkey, when these various drugs were applied to the surface of the uninjured brain and when injected into severely damaged brain.

A. THE EFFECT OF THE APPLICATION OF SULFONAMIDES TO THE UNINJURED CORTEX

Experimental procedure. Four Macaca mullata monkeys were used for this experiment, one for each of the drugs to be tested. Microcrystalline preparations of the various sulfonamides were applied to the cortex.

The entire procedure in each of the 4 animals was carried out under aseptic conditions and under local anesthesia with 1:1500 nupercaine. The monkeys were restrained relatively painlessly in a special holder.

Two holes, 6 millimeters in diameter, were made in the skull about 12 millimeters apart over the motor and sensory areas of each hemisphere.

From the Department of Neurology and Neurosurgery, McGill University and the Montreal Neurological Institute.

This study was carried out with the aid of the Subcommittee on Surgery of the Associate Committee on Medical Research of the National Research Council, Ottawa. Microcrystalline sulfonamides kindly furnished by Smith, Kline & French.

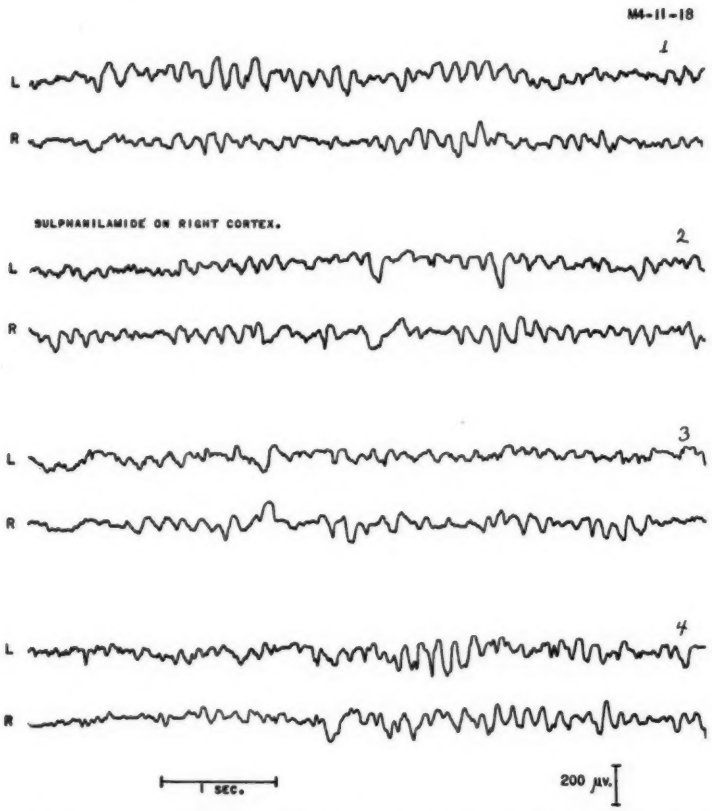

Fig. 1. Electroencephalograms taken with bipolar electrodes from pia-arachnoid over uninjured cortex, simultaneous recording from left and right sensory-motor regions. Sulfanilamide microcrystals were applied on cortex beneath electrodes on right hemisphere. Note absence of appreciable change in sample records *2* (after 9 minutes), *3* (after 2 hours, 20 minutes), and *4* (after 21 hours) compared to the control sample *1*.

The holes were then threaded. A circle of dura was removed under each hole, and avascular areas of the pia-arachnoid were pricked in several places with a fine needle, with care not to injure the underlying cortex. Then threaded leucite plugs carrying sealed silver electrodes were screwed into the skull and electroencephalographic tracings were taken to serve as control.

When the control record was completed, one plug was removed over the motor area of one hemisphere and a microcrystalline preparation of one of the sulfonamides to be tested was applied through the dural opening to the surface of the cortex. The plug was immediately replaced and electroencephalographic recording was begun at once. As well as the control record, before application of the drug, the simultaneous recording of the electrical activity from the opposite untreated hemisphere also provided a continuous control. The recordings were continued at varying intervals and up to 24 hours if they had shown no evidence of change.

Results of application to uninjured surface of the cortex. 1. Sulfanilamide. There was no change in the electrical activity of the cortex at any time within the 24 hours this animal was studied (Fig. 1). There was no evidence of even a depression in the amplitude of the normal rhythms. To assure that an adequate amount of the drug had been applied, further applications were made after 20

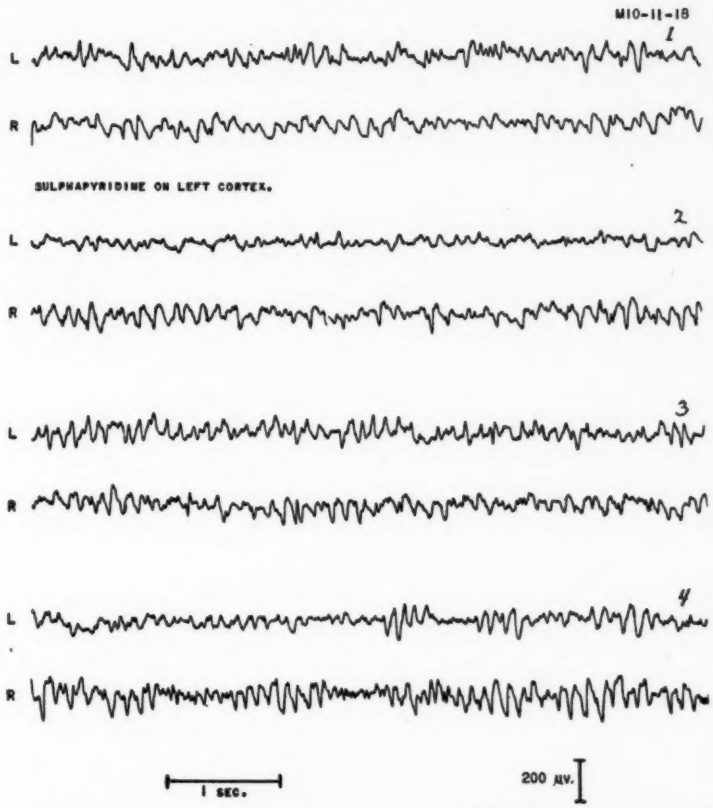

Fig. 2. Electroencephalograms taken with bipolar electrodes from pia-arachnoid over uninjured cortex. Sulfapyridine was applied beneath electrodes on the left side. Note absence of change in records *2* (after 4 minutes), *3* (after 2 hours, 20 minutes), and *4* (after 21 hours) as compared to control sample *1*.

hours, and this time microcrystals of sulfanilamide were placed in larger amounts than used initially beneath each one of the electrodes over the right hemisphere, whereas they had been placed on the cortex under but one initially. Still no change in electrical activity from this region was observed though recordings were carried out at intervals over a period of 4 hours.

The animal did not seem to be much disturbed by the procedure and was allowed to survive for experiments of other types.

2. Sulfapyridine. During the first 10 to 15 minutes following the application of sulfapyridine there was a slight depression of the normal activity of the cortex as compared with the control from this side and with the opposite cortex. However, the electrogram returned to normal in every respect within 2 hours (Fig. 2). Perfectly normal electrograms were obtained up to 21 hours after the application, when recording was continued. No slow waves or epileptiform discharges were recorded at any time. There were no clinical signs of cortical disturbance. The animal was released for experiments of a different nature and apparently none the worse for the experiment.

3. Sulfadiazine. The animal chosen for this experiment had been used 55 days before in an experiment, not included in this report, in which sulfonamides were applied to the wounded brain. He was chosen for the experiment because sulfathiazole had produced not only electroencephalographic evidence of focal seizures but also severe focal and general seizures which had continued at intervals for 1 week, after which time the seizures

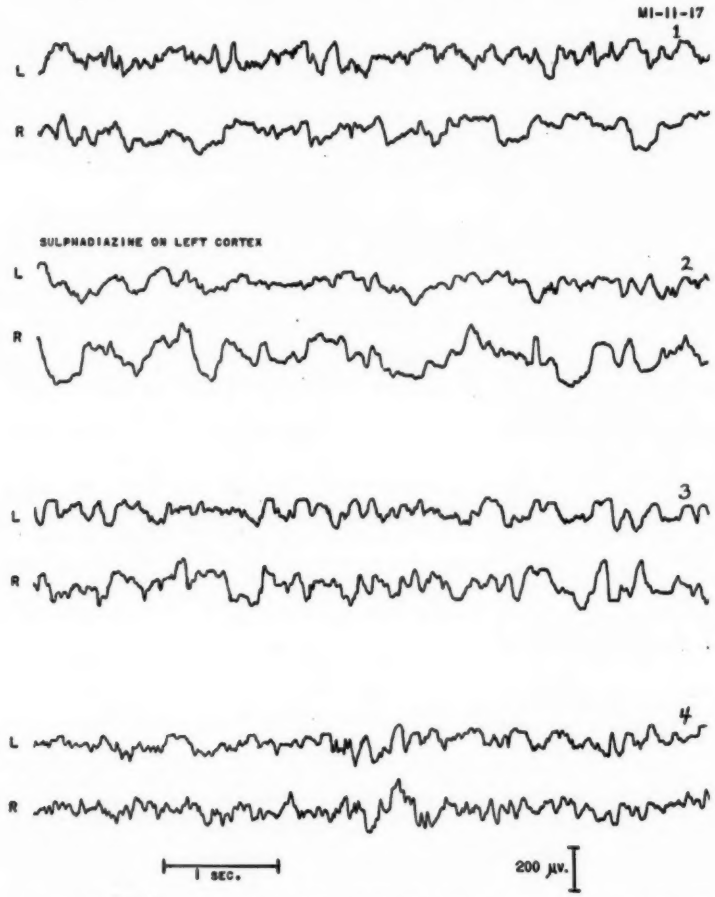

Fig. 3. Electroencephalograms taken with bipolar electrodes from the pia-arachnoid, left and right sensory-motor regions. Cortex had been injured near the posterior one of the pair of electrodes in previous experiments 55 days before, when this animal had convulsions in response to sulfathiazole. Sulfadiazine was applied beneath the anterior electrode which was over uninjured left motor cortex. There was no appreciable change in the electrogram as illustrated in samples *2* (after 2 minutes), *3* (after 5 hours), and *4* (after 24 hours); *1*, control.

stopped and the electroencephalographic tracings showed evidence of brain damage but no seizure waves. It was felt that the result after sulfadiazine would be doubly significant if negative, since the susceptibility to convulsion with sulfathiazole had been demonstrated. The cortical injury had been bilateral. The sulfathiazole had been placed on the right side only.

Two electrodes were placed anterior to the injured cortex on the right and left sides over the uninjured cortex. The control runs showed some slow wave activity, the result of the previous injuries most marked on the right side (Fig. 3).

Following the local application of microcrystalline sulfadiazine to the uninjured cortex on the left side, beneath the most anterior electrode, no appreciable change in the electroencephalographic tracing resulted. More drug was then applied, this time to the cortex underneath both electrodes on the left side, again with no effect on the trac-

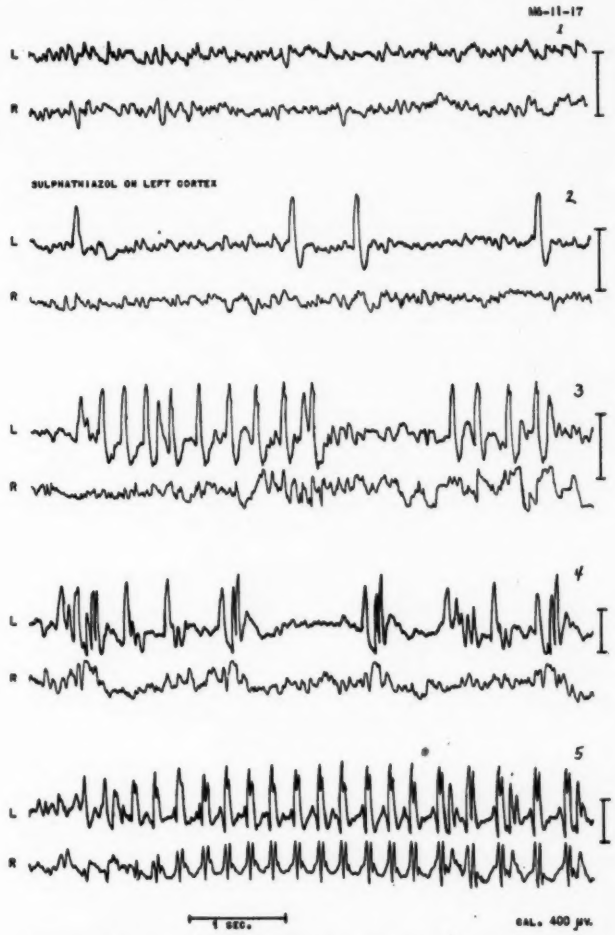

Fig. 4. Sulfathiazole applied to the left motor area over uninjured cortex produced large "spike-like" waves in 18 minutes as shown in sample *2*. In 27 minutes, *3*, Jacksonian attacks confined to the right hand and arm were seen to accompany the burst of epileptiform waves in the electroencephalogram. Within 5 hours, sample *5*, there was some spread of the seizure to the right hemisphere in the electroencephalogram and the left side of the body was also involved in convulsive movements. Calibrations at right equal 400 microvolts. Note reduction of sensitivity in samples *4* and *5*; *1*, control.

ings. Recording was continued at intervals over a period of 6 hours and then discontinued and the animal made an uneventful recovery.

4. Sulfathiazole. The animal used for this experiment had been used 55 days before for the experiment with sulfadiazine. Cerebral wounds had been produced in the posterior parietal regions on both sides and microcrystals of sulfadiazine had been injected into the damaged cortex on the right side. No changes in the electroencephalographic tracings of epileptiform nature were recorded, and the animal showed no abnormality in clinical examinations.

The electrodes were placed well anterior of the

area of previous brain damage, and the control records showed little evidence of abnormality and no epileptiform activity.

Eighteen minutes following the application of sulfathiazole, beneath the anterior electrode on the left side, large amplitude, isolated, negative spikes appeared from that area (Fig. 4). The electrical activity from the right homologous region was undisturbed at this time, and no clinical seizures were observed. After 25 minutes the epileptiform spikes became larger and were grouped together in bursts. Clonic movements of the right hand began to occur at this time, and there also appeared some disturbance in the normal activity of the opposite hemisphere shown by small sharp waves, apparently transmitted from the large spike discharges on the left side. Within 1 hour, the bursts of spike activity had become still more frequent and of greater amplitude, and the clinical seizures involving the right hand and arm were more forceful and lasted longer.

After 5 hours the focal seizures which had been limited to the right hand spread to the left side of the body and the attacks were generalized. This was shown in the electroencephalogram by synchronous spikes from the two hemispheres (Fig. 4, sample 5).

The clinical seizures continued for 4 days and then stopped and the animal made a good recovery.

SUMMARY

No appreciable change in the electrical activity of the cortex and no signs of cortical damage have been recorded or observed following the local application of microcrystalline sulfanilamide, sulfapyridine or sulfadiazine to the uninjured cortex. Microcrystalline sulfathiazole, however, produced a striking local irritation of the uninjured cortex within 18 minutes of its application. Electroencephalographic evidence of first focal seizures and then general ones have been recorded. Typical Jacksonian seizures and generalized seizures took place. Electroencephalographic evidence and behavior of the animal's seizures showed that the seizure storm always commenced in the area of the cortex to which the drug was applied.

B. THE EFFECT OF THE INJECTION OF MICROCRYSTALLINE SULFONAMIDES INTO DAMAGED CEREBRAL TISSUE

Experimental procedure. Four monkeys were used for this experiment, 1 for each of the drugs to be tested. Microcrystalline preparations of the various sulfonamides in a suspension made serum isotonic with sodium chloride, were injected into traumatized brain. Normal saline solution was injected into traumatized brain of the opposite hemisphere as a control.

The operative procedures were carried out under rigid aseptic conditions. The placement of leucite plugs carrying electrodes and trephine openings in the skull were made under nembutal anesthesia (.032 gram of nembutal per kilogram of body weight) given intraperitoneally. Trephine holes, 1 centimeter in diameter, were made in the skull over each parietal lobe. The recording leucite plugs carrying the electrodes were screwed into the skull near the anterior and posterior borders of the trephine openings. The dura was not incised except by accident under one recording electrode in 1 animal. The scalp incisions were closed in layers about the electrodes.

The animals were left for 24 hours to recover from the anesthesia before electroencephalographic recordings were begun. At this time they were feeding and seemed normal.

The recordings were done with the animal restrained in a special holder without anesthesia. Control records were taken from each hemisphere and then with aseptic technique, needles were passed through the scalp over the trephine openings and through the dura into the brain for a depth of about 6 millimeters. The needle points were then roughly manipulated with a rotary movement to damage the cortex on each side. One cubic centimeter of normal saline was injected through the needle on the side to be used as a control and 1 cubic centimeter of a 10 per cent suspension of microcrystalline sulfonamides through the needle on the other side. Electrical recordings were begun at once.

1. Sulfanilamide. The electroencephalographic tracings of cortical activity were changed after the brain damage, and by the injection of saline on the one side and sulfanilamide on the other. One minute after the injection, normal rhythms were absent on both sides (Fig. 5). Depression in amplitude of electrical activity was most marked on the side of the sulfanilamide injection and the depression lasted longer on this side. This depression began to disappear in about 2 hours. Within 6 hours the electroencephalograms from the two sides were indistinguishable and no abnormal waves were observed of an epileptiform type; the only abnormal waves present being those characteristic of brain injury. The final electroencephalograms on this animal were taken 24 hours after the injection, and the records obtained were essentially the same as those recorded 6 hours after the wounding and the injections.

The conclusion from this experiment then, was that sulfanilamide did not increase the evidence of

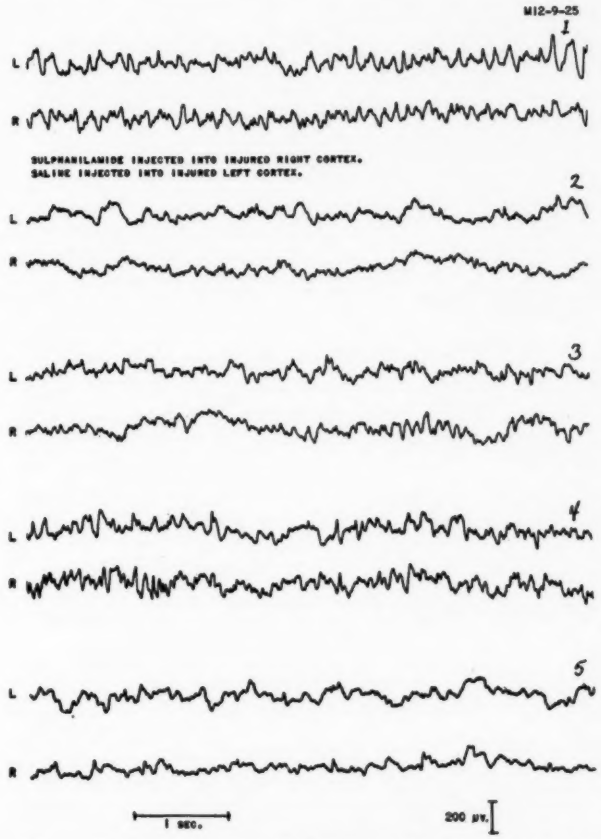

Fig. 5. Electroencephalograms before, *1*, and after injection of 1 cubic centimeter of 10 per cent suspension of microcrystalline sulfanilamide into injured brain, right parietal area, and control injection of 1 cubic centimeter normal saline into injured left parietal area. Note slight depression in amplitude of electrical activity in samples *2* (after 48 minutes), and *3* (after 2 hours, 8 minutes), but no evidence of excitatory action. *4*, six hours, 46 minutes; *5*, 24 hours.

injury, did not cause epileptiform discharges, but did perhaps cause a slight depression in the amplitude of activity for a longer period than did brain injury and normal saline injection. The animal recovered without incident.

2. Sulfapyridine. Electroencephalograms taken 1 minute following the brain wounding, the injection of saline on the control side, and 1 cubic centimeter of a 10 per cent suspension of microcrystalline sulfapyridine, showed large amplitude, slow continuous waves whose frequencies were between 1 and 2 per second, replacing completely the normal rhythms on the side of the drug injection (Fig. 6). There was relatively little immediate change in the right hemisphere which had been wounded and injected with 1 cubic centimeter of normal saline.

After 25 and 30 minutes the slow waves had increased in amplitude from the drug side, and low amplitude slow waves intermingled with normal rhythms from the saline control side.

At 5 hours the tracings began to show some more rapid sharp waves from the drug side.

The records taken 24 hours after the drug showed a few random spikes characteristic of epileptic discharges though they were always moderate in amount and of low amplitude.

Electroencephalograms 6 days, 15 days, and 25

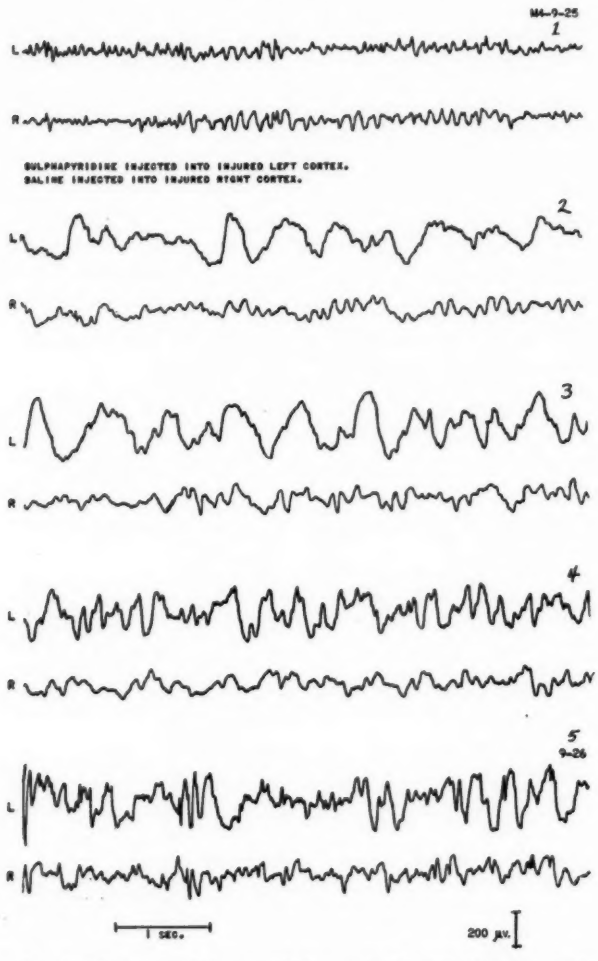

Fig. 6. Electroencephalograms before and after injection of 1 cubic centimeter of 10 per cent suspension of microcrystalline sulfapyridine into the injured left parietal area and control injection of 1 cubic centimeter of normal saline into the injured right parietal area. Large slow waves appeared immediately from drug injected side, sample *2* (after 2 minutes), and became somewhat epileptiform after 25 hours, sample *5*. This does not occur without injury (see Fig. 2). *1*, control; *3*, after 27 minutes; *4*, 5 hours, 15 minutes.

days later all showed occasional episodes of moderate amplitude epileptiform activity from the anterior border of the injured sulfapyridine injected hemisphere. There were some low amplitude waves of the same form from the injured saline injected hemisphere. This animal had made an uneventful recovery after the experiment and had never been observed to have clinical seizures.

It was noted at the time of injecting the drug that the injury to the brain produced on this side would probably be greater than on the saline control side. This fact, together with the persistence of abnormal electrical activity 55 days after the injection, indicates that the abnormal discharges were probably due to the wound rather than to sulfapyridine. The 100 milligrams of

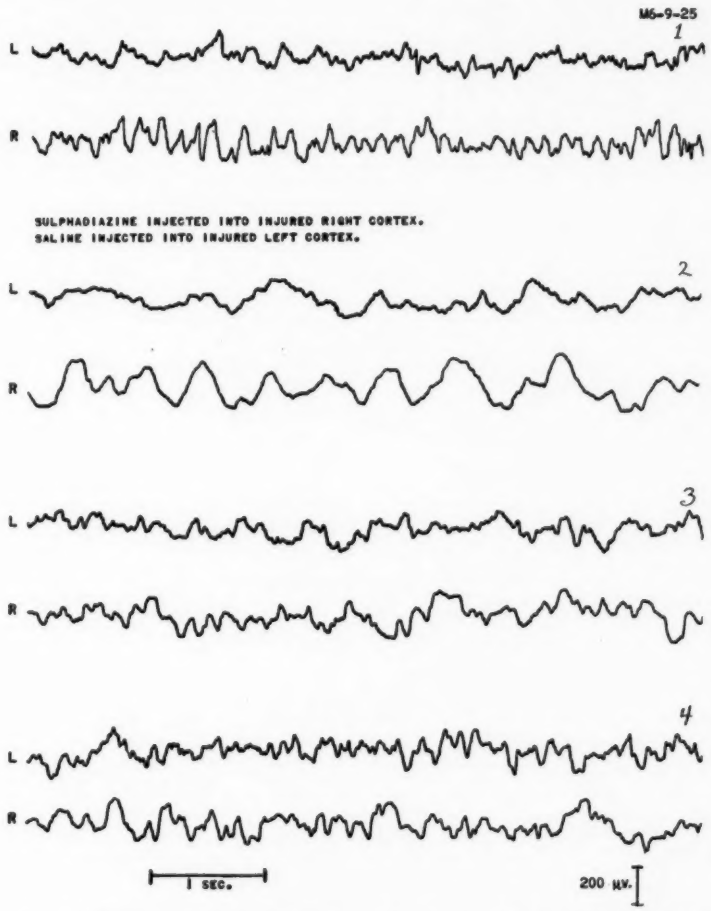

Fig. 7. Electroencephalograms before and after injection of 1 cubic centimeter of 10 per cent suspension of microcrystalline sulfadiazine into injured right parietal area and 1 cubic centimeter normal saline into injured left parietal area. Slow waves replaced normal rhythms immediately following injury, more from the drug injected side, sample *2*. Results of injury were about equal in samples *3* and *4* taken 2 hours 8 minutes and 13 days following injury. *1*, control.

sulfapyridine injected would have been expected to be absorbed long before the last tracings were taken. The conclusion that the spike discharges were not due to sulfapyridine, but to the wound alone, is supported by the fact that the direct application of sulfapyridine to the uninjured cortex caused no seizure waves in other experiments.

3. Sulfadiazine. Within the first half hour after wounding and the injection of 1 cubic centimeter of physiological saline on the control side and 1 cubic centimeter of a 10 per cent suspension of sulfadiazine on the other side, there was an increase in slow wave activity on the side injected with the drug (right) and to a lesser extent on the control side (left) as shown in the second sample (Fig. 7).

After 2 hours the recordings from the drugged side and from the control side were essentially the same, and they remained the same when tested at intervals up to 13 days following the injection.

There were no clinical signs of cerebral disturbance at any time after operation, and it was this animal which was chosen to be used in the experi-

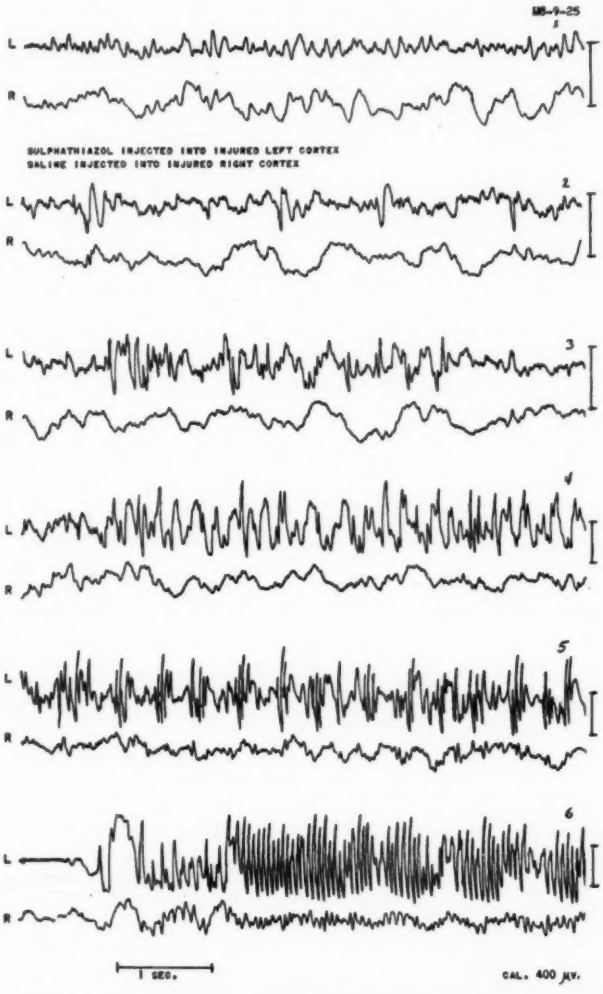

Fig. 8. Electroencephalograms before and after injection of 1 cubic centimeter of a 10 per cent suspension of microcrystalline sulfathiazole into injured left parietal area, and injection of 1 cubic centimeter normal saline into injured right parietal area. The right parietal area was accidentally injured before the control record, sample *1*, causing random slow waves to appear. Local epileptiform waves from the drug injected side increased in amount during first 5 hours, samples *2* (25 minutes) *3* (44 minutes) and *4*. In 23 hour and 4 day samples, *5* and *6*, there was evidence of transmission of epileptiform activity to the opposite hemisphere, and animal was having generalized convulsions, beginning on the right side. Calibration at right of samples equals 400 microvolts. Note reduction in sensitivity for samples *4* (5 hours, 10 minutes) to *6* (4 days).

ment carried out 55 days later with sulfathiazole on the uninjured cortex.

4. Sulfathiazole. In this animal an accidental injury to the brain had been made under one of the recording electrodes as it was being inserted. This caused slow waves to appear in the control

electroencephalographic records taken before the drug was injected. The injury was on the *right* side (first sample of Fig. 8). Because of this, the drug was injected into the wound made with the hypodermic needle in the *left* hemisphere. One cubic centimeter of a 10 per cent suspension of microcrystalline sulfathiazole was injected. A similar wound was made with a hypodermic needle on the right side, in spite of the previous accidental wounding, and 1 cubic centimeter of physiological saline was injected into this wound.

Within the first 5 and 10 minutes after the bilateral injuries and the injections, there was a progressive increase in the slow wave activity from both sides. After 15 minutes the amplitude of the electrical activity was increased on the side of the injection of the drug, and a few low amplitude epileptiform spikes appeared. Over the next 20 minutes these isolated spikes increased in amplitude and frequency. Forty minutes after the injection bursts of epileptiform spikes appeared from the left side which were several seconds long (Fig. 8, sample 3). The epileptiform activity gradually increased during the first 5 hours from the region where sulfathiazole had been injected. There were no convulsive movements of the animal during the first 5 hours of recording (Fig. 8, sample 4), but during the electroencephalographic bursts of spikes the animal's gaze would become fixed and this would be followed by blinking of the eyes (the drug was injected into the posterior parietal region, not near the motor area).

The next morning, 23 hours after the experiment was begun, the animal was having frequent seizures which began in the right hand, spread over the right side and frequently, in the more severe attacks, spread to the left side. Recordings taken at this time showed prolonged episodes of very large amplitude multiple spike discharges from the left hemisphere with some evidence of transmission to the right side (Fig. 8, sample 5). Four days later, the animal was still having frequent and severe seizures and records showed the epileptic activity had increased in the left hemisphere and was showing more spread of these waves to the right side where they were, however, of lower amplitude.

The convulsions in this animal continued to increase in severity and as the general condition was deteriorating, the animal was killed 5 days after the drug was injected. The dura was tense, and the convolutions were flattened. This was due to considerable hemorrhage in the brain wounds made with the hypodermic needles on both the right and left sides. The findings were sufficient, it seemed, to account for the unfavorable course. It is not felt that the hemorrhages vitiate the experiment but they do complicate it.

In conclusion sulfonamides act on injured cerebral tissue as they do when applied to the uninjured cerebrum. It was inevitable that the electroencephalograms in the two sets of experiments were not entirely comparable. In the animals with wounds there is evidence of the wounding and also changes as the result of the increased pressure after the injection of the physiological saline on the one side and the suspension of the drug on the other. Sulfathiazole was the only one of the four drugs which produced epileptiform discharge in the electroencephalogram and convulsive seizures in the animal.

EVALUATION

One of the most careful and significant articles we have discovered on the antibacterial action of sulfonamides in infected wounds is by Green and Parkin. They point out that the view that different sulfonamides are specific for different organisms is now held to be fallacious. The effect of the different sulfonamides on any species is dependent on the ability of the compound to block enzymes whose substrate is para-aminobenzoic acid. Their mode of *in vitro* activity parallels in most instances their action *in vivo*. The action is directly antibacterial therefore, and it is due to this and not to any direct action on body tissues generally that infection is controlled. *In vitro* tests carried out by these authors have shown that sulfanilamide, sulfapyridine, and sulfathiazole required increasing amounts of para-aminobenzoic acid to block their antibacterial activity. They suggested that a tentative evaluation of the efficiency of the 3 compounds as measured by the *in vitro* test is 1 for sulfanilamide, 5 for sulfapyridine, and 50 for sulfathiazole. They did not carry out *in vitro* tests with sulfadiazine and no reports could be found in the literature permitting the antibacterial activity of sulfadiazine to be evaluated so definitely as the results obtained by Green and Parkin for the other drugs. Spinks' report of *in vitro* studies does show the efficiency of sulfadiazine to be much greater than sulfanilamide and sulfapyridine but less than sulfathiazole.

Since sulfathiazole has been shown to have the greatest *in vitro* power to inhibit bacterial growth, it should therefore be the most potent drug in potentially infected and infected wounds of the brain. Our experiments, however, have provided evidence agreeing with the findings of Pilcher's group and those of Watt and Alexander that sulfathiazole, even in small amounts, may cause convulsive seizures when it is applied to the intact

or wounded cerebral cortex. We have described experiments on 2 monkeys in some detail where electroencephalographic studies of the changes in cortical activity preceding the actual development of clinical seizures have been followed in unanesthetized animals. Actual seizure and electroencephalographic evidence, showing that they have developed from the brain at the site of the application of this drug, have been studied also in cats and still other monkeys. While clinical seizures have not occurred following the application in every experimental animal, electroencephalograms have always shown either excitation or epileptiform waves.

The solubility of sulfathiazole in serum at 37 degrees centigrade is given as 184 milligrams per cent by Lyons and Burbank. Because sulfathiazole altered brain waves in such a relatively short time after its application to the brain, it seemed that the effect might occur at much lower concentrations than maximum saturation. If this impression were correct, nerve cells might be exposed by intravenous injections to sulfathiazole blood levels which would irritate, and even cause, seizures.

In 2 monkeys, without anesthesia, convulsions were produced by the intravenous injection of the sodium salt of sulfathiazole. Electroencephalographic records were taken before and during successive injections, and samples of blood were taken at intervals for the determination of blood concentration.

In the first experiment, facilitation of cortical discharge was apparent in the electroencephalogram when the blood level reached 18 milligrams per cent of free and 25 milligrams per cent total sulfathiazole. However, it was not until the blood levels reached 84 milligrams per cent free and 110 milligrams per cent total that a sudden burst of large epileptiform waves appeared in the electroencephalogram and the animal had a major convulsive seizure. The animal then went rapidly into severe status epilepticus.

In the second monkey the first evidence of cortical facilitation appeared in the electroencephalogram when the blood levels were 37 milligrams per cent free and 52 milligrams per cent total, respectively. Again marked epileptiform discharge with convulsions did not appear until very high blood levels were reached, 89 milligrams per cent free and 123 milligrams per cent total, respectively.

From these 2 experiments on unanesthetized monkeys it appears that the concentration of sulfathiazole in the blood stream must reach at least 80 milligrams of the free drug with a total concentration of 110 milligrams per cent before convulsions are produced. That these convulsions were not due to alkalosis was proved in the first animal by carbon dioxide combining power determination in the serum.¶ When the blood level had reached its maximum, the carbon dioxide combining power was 65.4 volumes per cent. This problem warrants further investigations, for it may have considerable clinical significance.

Sulfadiazine, next to sulfathiazole in its *in vitro* potency, has been found to have little, if any, effect on the electrical activity of the cortex in monkeys. No excitatory activity or epileptiform spikes resulted from its use and clinical seizures have not been observed in the animals.

Sulfapyridine, the *in vitro* antibacterial activity of which is said to be 10 times less than sulfathiazole, we feel is not epileptogenic or excitatory, and, on the encephalographic evidence, would not hesitate to support its uses on the human cerebral cortex. Other factors, however, make it undesirable; its low solubility and the fact that its activity does not approach that of sulfadiazine and is estimated to be but 5 times the potency of sulfanilamide.

Sulfanilamide, aside from slight depression of the electrical activity, has no undesirable electrical side effects. It does not stimulate or cause epileptiform waves. Its solubility makes it a valuable adjunct to use in connection with sulfadiazine.

For contaminated and potentially infected and infected wounds of the brain, sulfapyridine may be discarded because it is not as efficient an antibacterial agent as sulfadiazine and less soluble than sulfadiazine. Sulfathiazole is epileptogenic and contraindicated. A combination of sulfanilamide and sulfadiazine for wounds of the brain would seem on the basis of experimental evidence, gained from this study and from the histological and bacteriological studies of others, to be the drugs of choice. Used in combination a high concentration of the more soluble sulfanilamide is obtained early, and the more efficient, but the more insoluble, sulfadiazine provides for prolonged action.

In these studies sulfonamides have been used singly and not in combination. We have used them in combination on the human brain. For the most part, combinations of sulfanilamide and sulfapyridine have been used but also sulfanilamide and sulfadiazine. In a few patients a mixture of sulfanilamide, sulfapyridine, and sulfathiazole have been applied directly to the brain without the subsequent production of epileptic

seizures. This raises the question of the possible suppression of the epileptogenic potency of sulfathiazole when used in combination with other sulfonamides. Experiments designed to test this hypothesis are now in progress.

Though it may seem to be out of place in this paper, it is important to point out again that these compounds act as foreign bodies in the brain, and they should always be used circumspectly and, of course, should be sterile.

SUMMARY AND CONCLUSIONS

The effect of microcrystalline preparations of sulfanilamide, sulfapyridine, sulfadiazine, and sulfathiazole applied to the surface of the uninjured cerebral cortex or injected into the injured brain of unanesthetized monkeys has been studied with electroencephalographic records taken from the surface of the dura or pia-arachnoid. The effect of the intravenous administration of the sodium salt of sulfathiazole upon the electrical activity of the cortex was also studied in unanesthetized monkeys.

1. Sulfathiazole applied directly to the cerebral cortex has a marked excitatory action causing local epileptiform discharge and convulsions which develop into severe generalized epileptic seizures.

2. Sodium sulfathiazole, injected into the blood stream, will produce epileptic convulsions only after the concentration of unconjugated drug has exceeded 80 milligrams per cent with a total concentration of over 110 milligrams per cent. Definite excitatory effects may be observed in the electroencephalogram with blood levels ranging between one-quarter and one-half these amounts.

3. Sulfanilamide, sulfapyridine, and sulfadiazine applied to the uninjured cortex cause no detectable change in its electrical activity nor any clinical evidence of altered function. Injected into the injured cortex these drugs cause a slight transient depression of electrical activity or a transient increase in the amount of slow wave activity following the injury, but no evidence of excitatory or epileptogenic action.

4. A combination of sulfanilamide and sulfadiazine is suggested as the preparation of choice for topical application to the brain on the basis of relative solubility, antibacterial action, and freedom from irritative action on cerebral tissue.

5. Sulfathiazole should not be used on the human brain.

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TANNIC ACID AND LIVER NECROSIS

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WELLS, Humphrey, and Coll have reported recently that subcutaneous administration of tannic acid results in liver necrosis in rats. They suggest that it does not seem improbable that the liver necrosis noted in many cases of severe burns may have been due to the toxic action of the tannic acid used in treatment rather than to toxic products arising from the burned tissue. Because of the widespread use of tannic acid in the treatment of burns, it was our opinion that confirmation of this work would be justified at this time. In addition, since the liver damage resulting from tannic administration is central and somewhat similar to that given by carbon tetrachloride, it was decided to study the possible protective action of sulfanilamide on tannic acid liver necrosis. Previous investigations by Forbes and associates (2, 3) and others (4) show that oral administration of sulfanilamide increases the resistance of rats to both acute and chronic carbon tetrachloride poisoning. This protective action of sulfanilamide on the liver has also been found in acute chloroform poisoning in rats (1).

EXPERIMENTAL

Series 1. Thirty milligrams of sulfanilamide per 100 grams of body weight was given by stomach tube to 4 rats late in the afternoon. This was followed immediately by the subcutaneous injection of 50 milligrams of tannic acid (U.S.P. granular) per 100 grams of body weight. The needle was always inserted about the middle of the back and the injection made just back of the neck. Similar amounts of tannic acid were given to 4 control animals. The sulfanilamide and tannic acid administrations were repeated next morning and on two additional mornings thereafter. The animals were sacrificed 24 hours after the last injection, and histological examination of the livers were made. All livers showed definite areas of necrosis and no apparent difference could be seen between those of the control and treated animals.

Series 2. Thirty milligrams of sulfanilamide per 100 grams of body weight was given by stomach tube to 4 rats about 9:00 a.m. This was followed immediately by the subcutaneous injection of 1 cubic centimeter of a 10 per cent solution of tannic acid per 100 grams of body weight. Four control animals were given a corresponding amount of tannic acid. The sulfanilamide and tannic acid administrations were repeated next morning. All of the animals were sacrificed 24 hours after the last injection and their livers were examined histologically. Although there was no marked difference between the livers of the two sets of animals, those given sulfanilamide in addition were, if anything, slightly worse than those from the controls.

Series 3. Thirty milligrams of sulfanilamide per 100 grams of body weight was given by stomach tube to 4 animals about 9:00 a.m. Next morning another similar dose of sulfanilamide was given to the same rats. This was followed immediately by the subcutaneous injection of 1 cubic centimeter of 10 per cent tannic acid per 100 grams of body weight to these animals and to 4 untreated control animals. All were sacrificed 48 hours after this injection. On histological examination of the livers, those from the animals receiving sulfanilamide in addition to the tannic acid were slightly worse than those of the controls.

Series 4. Thirty milligrams of sulfanilamide per 100 grams of body weight was given to 10 animals by stomach tube. This was followed immediately by the subcutaneous injection of 1 cubic centimeter of a 15 per cent solution of tannic acid per 100 grams of body weight. Similar amounts of tannic acid were injected into 10 control animals. Five of the rats receiving sulfanilamide and 2 of the controls were dead 18 hours later. Another control was found dead 24 hours later. All the remaining animals were sacrificed 48 hours after the tannic acid injections and their livers examined histologically. The livers of the sulfanilamide treated animals which survived were on the whole somewhat better than those of the surviving controls. However, in view of the fact that 50 per cent of the treated animals and only 30 per cent of controls died, it appears that the differences noted histologically were incidental rather than the result of sulfanilamide administration.

Series 5. Although the oral administration of sulfanilamide exerted no protective action against

From the Departments of Biochemistry and Surgery, Medical College of Virginia. This study was conducted under a grant from the Committee on Medical Research, Office of Scientific Research and Development.

the hepatotoxic action of tannic acid, it does not necessarily follow that similar results would be obtained if the two were injected subcutaneously in a single solution. Consequently, 1 cubic centimeter per 100 grams of body weight of a 12.5 per cent solution of tannic acid containing 30 milligrams of sulfanilamide, partly in solution and partly in suspension, per cubic centimeter, was injected subcutaneously into 5 rats. A similar amount of tannic acid without sulfanilamide was injected into 5 control animals. The animals were killed 48 hours after injection and their livers were examined histologically. Although there were no marked differences between them, the livers of the animals receiving sulfanilamide with the tannic acid were slightly worse than those of the control animals.

Series 6. Since subcutaneous xanthine injection is known to increase a rat's resistance to the hepatotoxic action of carbon tetrachloride (5), it was decided to determine if it would have a similar action against tannic acid. One hundred milligrams of a xanthine suspension in water per 100 grams of body weight were injected subcutaneously just back of the tail, into 4 rats. Forty-eight hours after they, along with an equal number of controls, were given an injection of 1 cubic centimeter, of a 12.5 per cent tannic acid solution per 100 grams of body weight. All the animals were sacrificed 48 hours later, and their livers were histologically examined. No evidence of any protective action from the xanthine injections was obtained.

OBSERVATIONS

Tannic acid administration to the rat appears to give a fairly uniform and rather specific liver lesion. In most of the sections studied in these experiments the necrosis of the liver was almost always central with the remainder of the liver lobule, especially the periphery, remaining almost normal. We have not seen in our sections the numerous mitotic figures described by Wells but there has been infiltration of the interstitial tissue with leucocytes. Figure 1 illustrates a typical section of liver of a rat which has received 1 cubic centimeter of a 12½ per cent solution of tannic acid per 100 grams of body weight. It is representative of most of the sections obtained in this study.

It is disappointing that we found no protective action of any of the substances studied against the hepatotoxic action of tannic acid. Substances which give fairly good protection against carbon tetrachloride and chloroform, such as sulfanilamide and xanthine, afford practically no protection against tannic acid. For this reason we are inclined to the view that the mechanism of action of tannic acid may be quite different from that of chloroform and carbon tetrachloride. In a search for substances that might possibly protect the liver against tannic acid poisoning, the studies herein reported indicate that investigations should not be limited to those substances that protect the liver against carbon tetrachloride and chloroform poisoning. In other words, it is more than likely that high carbohydrate and high protein diets will afford no protection to the liver of a burn patient who has been treated with tannic acid.

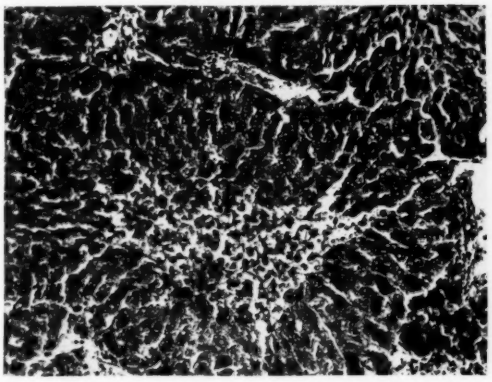

Fig. 1. Typical section of the liver of a rat given 1 cubic centimeter of a 12½ per cent solution of tannic acid per 100 grams of body weight.

SUMMARY

The hepatotoxic action of subcutaneous tannic acid injections has been confirmed. No protective action was given, either by the oral or subcutaneous administration of sulfanilamide or the subcutaneous administration of xanthine.

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INJURIES TO THE LARYNX AND TRACHEA

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INJURY to the larynx and trachea, though not uncommon, is infrequently reported in the literature. Since these cases are ordinarily handled at the outset by the general surgeon, the material is offered from such a perspective. The following is based on a study of 17 cases of injury to the laryngotracheal passage treated by the surgical service of the Harlem Hospital in the past 10 years. Fourteen of these were various direct wounds of the larynx or trachea, whereas 3 were of the subcutaneous rupture type.

The greater number of reports that have appeared in the literature have dealt principally with the subcutaneous rupture type. Isolated instances of cut throat or laceration of the trachea or larynx have been described. Scott described what he believed to be the first reported case of complete division of the trachea and esophagus, the result of accidental injury. In this instance the divided esophagus, trachea, and soft parts were successfully united by primary suture. Bailey reports his experience with 57 cases of cut throat. Zeuch in presenting a case of subcutaneous rupture of the trachea tabulated the results of 52 similar cases found in the literature up to that time.

ETIOLOGY

A. Lacerations. Although suicidal attempts are by far the most frequent cause, there are various other mechanisms, some of which may be quite bizarre. In the majority of lacerations of the neck requiring surgical aid, vital structures remain uninvolved, the trauma being confined to the skin, platysma, or neck muscles. The movability and resiliency of the trachea and larynx undoubtedly preclude greater frequency of injury to these parts. The limited protection afforded by the chin, sternum, and lateral neck musculature tends to restrict the incidence of injury.

B. Subcutaneous rupture. Subcutaneous injury to the upper air passages, though usually the result of direct trauma, may be due to indirect violence. Sunderland reported the case of a boy who in fright suddenly threw his head backward with resultant subcutaneous rupture of the trachea. Andre described a similar injury in a 19 year old primipara occurring during the course of a severe labor. Latour, Bredschneider, and Gesheid each described instances of subcutaneous rupture resulting from severe coughing spells. In Leffert's case the injury followed expulsive efforts to remove a foreign body in the trachea. Nixon reported a most unusual case of spontaneous rupture of the trachea with no describable cause. The onset was that of a spontaneous, rapid, crepitating swelling which simulated a large goiter and which became larger with expiration and smaller with inspiration. Shortly afterward spontaneous rupture of the skin occurred posterior to the right angle of the jaw, with 2 other ruptures in the vicinity of the right axilla. Exploration of the neck showed the rupture to have been in the thoracic portion of the trachea. A low tracheotomy was followed by an uneventful recovery.

One explanation for such occurrences is the mobility of the neck, which is surmounted by a top-heavy pendulous head. Zeuch believes that an important predisposing factor is the increase of intratracheal pressure due to holding of the breath, and that this is produced by closure of the epiglottis, a physiological reflex occurring at times of physical stress. Under such circumstances it is conceivable how direct or indirect trauma may produce a rupture of this hollow inflated viscus, a situation analogous to the comparative case of traumatic rupture of a distended urinary bladder. Desjacques and associates describe a case of a comminuted fracture of the trachea in a 70 year old male, the result of a horse kick which was successfully treated by emergency tracheotomy. Because of the lateral mobility of the trachea it is obvious that a damaging blow ordinarily must be directed in an anteroposterior direction so as to compress the part against the rigid spinal column.

PATHOLOGY

The pathological condition will vary with the nature and degree of the trauma. The lacerations or rents will be either transverse, oblique, or vertical, the transverse type being the most common. When the inflicting agent has a sharp edge, such as a razor or a piece of glass, the tracheal or laryngeal wound is likely to be a cleanly divided one. More crude instruments of trauma and crushing injuries will produce rents or fractures. The interannular membrane alone may be divided, the car-

From the Surgical Service of the Harlem Hospital, Dr. Clarence Howley, director.
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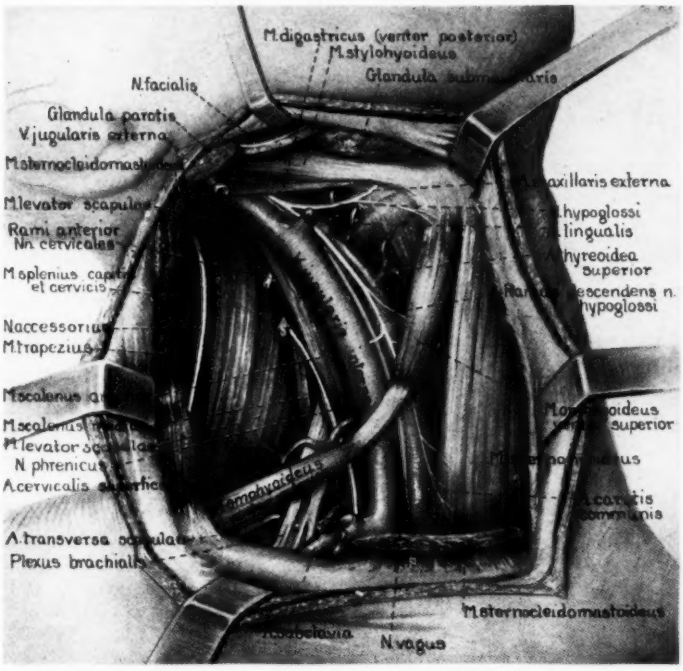

Fig. 1. In the lower portion of the neck the great vessels are much closer to the surface so that at the same depth a laceration, which higher up would not be serious, would be apt to injure one or more of these vessels. (From Callander's *Surgical Anatomy*, 2d ed., 1939. Saunders.)

tilaginous portions of the tracheal rings remaining intact. Perforations may result from gunshot injuries or puncture wounds. Tracheal fractures are apt to be irregular and occasionally are comminuted. Subcutaneous rupture can result without evidence of injury to the skin or soft parts, and may occur as low as at the bifurcation of the trachea. Varying portions of the trachea or larynx may be torn away by shot, shell, or other severe forms of trauma.

Bailey divides injuries to the laryngotracheal tract into 5 groups according to the anatomical location of the trauma, namely: (1) wounds above the hyoid bone; (2) wounds of the thyrohyoid membrane; (3) wounds of the thyroid cartilage; (4) wounds above, below or through the cricoid cartilage; and (5) wounds of the trachea.

Associated injuries to the esophagus, pharynx, blood vessels, or contents of the carotid sheath are as likely to occur as not. Death may follow promptly before adequate surgical treatment can be rendered. Bleeding may be severe, and in the case of subcutaneous rupture reported by Taylor, death was due to drowning by blood which filled the lower end of the trachea, the bronchi, and the bronchioles. Following complete division of the trachea, retraction of the ends usually follows and the lower part may disappear behind the sternum. With a severe contusion, submucosal hemorrhage, occasionally severe enough to occlude the lumen of the trachea, might result. Post-traumatic edema of varying degree may ensue with partial or complete obstruction to the airway.

The likelihood of injury to the contents of the carotid sheath will depend upon the level of the trauma. In the upper part of the neck, the great vessels are deeply situated and frequently escape injury. In the lower portion they are much closer to the surface so that the same depth of a laceration which higher up might not be as serious would, at this level, injure one or more of the great vessels of the neck. Hemorrhage from such associated large vessel trauma frequently will be fatal before surgical aid can be offered.

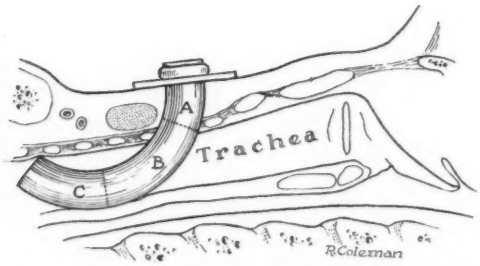

Fig. 2. Composite view of tracheal cannulas: *a*, too short; *b*, proper length; *c*, too long, as it permits end of cannula to impinge against wall of trachea.

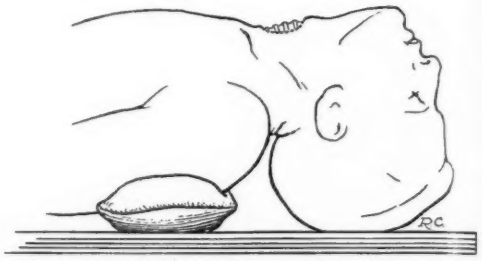

Fig. 3. Proper position for surgical procedures on the trachea. The sandbag or folded sheet is placed underneath the shoulders and not behind the neck. The head is fully extended so that the chin and sternal notch are in the same straight line.

SYMPTOMS

When the tracheal or laryngeal wound communicates with the skin surface, the nature of the injury and the respiratory rush of air and bloody froth through the wound make the situation quite apparent. Dyspnea, cyanosis, and cough will be present in varying degrees.

The subcutaneous rupture type is usually characterized by the prompt appearance of symptoms, the most common of which is a rapidly spreading subcutaneous emphysema. The latter is often out of proportion to the degree of injury. The earliest clinical manifestation of a rupture of the intrathoracic trachea is likely to be a subcutaneous emphysema appearing in the suprasternal notch (15). Occasionally there may be an appreciable interval before the onset of symptoms, as in the case described by Jackson and Jackson, in which a subcutaneous injury to the trachea did not make itself clinically evident until several hours had elapsed. The subcutaneous emphysema may appear and extend with such rapidity as to involve the entire body including the eyelids and scrotum within an hour or two. With the subcutaneous type of injury, particularly if there is tearing of the tracheal mucosa, localized pain, dyspnea, cough, cyanosis, wheezing, and a bloody mucoid expectoration are the chief signs. Should the lesions be at the level of the larynx, inspiratory retraction of the suprasternal notch, characteristic of laryngeal obstruction, will become manifest. Palpation of the neck occasionally may disclose an alteration in the normal contour of the larynx or trachea, or even separation of the divided tracheal ends. Ecchymosis, edema, or hemorrhagic infiltration of the soft tissues of the neck may be variable features. Hoarseness or aphonia commonly accompany laryngeal trauma because of the associated submucosal hemorrhage and edema.

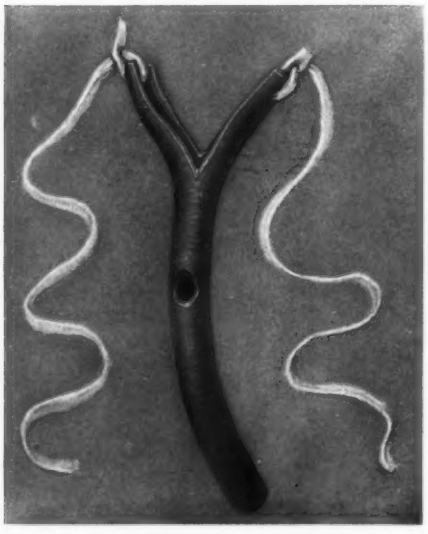

Fig. 4. A cannula that can be improvised from a piece of hard rubber tubing, should the need arise.

The danger in the use of morphine under such circumstances must be emphasized. Its administration, by alleviating respiratory distress and dyspnea, may be responsible for a failure of, or a sorry delay in, diagnosis. Unrecognized asphyxia due to edema, intratracheal hemorrhage, or submucosal hematoma may result from such narcosis.

DIAGNOSIS

When a gaping wound is present, the diagnosis is self-evident. With the subcutaneous type of injury, a history of direct or indirect trauma in conjunction with the group of symptoms previously described, namely, subcutaneous emphysema, cough, dyspnea, respiratory distress and bloody

mucoid expectoration, should indicate the probability of injury to the trachea or larynx. When the necessity for a positive diagnosis exists, direct laryngoscopy or bronchoscopy is indicated. Such a procedure is not only of great value in establishing a diagnosis, but will afford immediate relief from any obstructive dyspnea. X-ray study is helpful in diagnosis. It may reveal a clinically unrecognized subcutaneous emphysema or disclose some abnormality in the contour or position of the trachea. Dyspnea, following trauma to the neck, with or without other symptomatology, should lead one to consider seriously injury to the air passage. With obstruction of the larynx or upper trachea, a laryngeal type of dyspnea characterized by inspiratory retraction of the suprasternal and supraclavicular fossae will be evident. Swelling, hemorrhagic infiltration, or subcutaneous emphysema of the neck may obscure such inspiratory retraction. The diagnosis of intrathoracic rupture or fracture of the trachea or one of the bronchi may be extremely difficult, for the signs and symptoms may be masked by associated injuries which are usually severe.

Fracture of the hyoid bone and larynx. Fracture of the hyoid bone, though apt to involve any portion of the bone, usually occurs in one of the greater cornu, at or near the junction of the latter with the body. Considerable displacement of the fragments without perforation into the pharynx is not unusual. The condition is recognized by (1) the local findings of deformity, swelling and discoloration; (2) local pain on protruding the tongue or opening the mouth; (3) dysphagia, dysphonia, and hoarseness; and (4) distressing cough.

With fractures of the thyroid or cricoid cartilages, the symptoms are similar, but pain on swallowing is usually more intense. Dyspnea or cyanosis are prominent features. Palpation will reveal anatomical displacement unless obscured by hemorrhage or edema.

Reduction of a fractured hyoid bone can be attempted by placing the finger of one hand in the mouth, and then externally manipulating the fragments with the other hand. With a fracture of the larynx, tracheotomy is imperative once the diagnosis has been established, even though the dyspnea and cyanosis are not very marked. Attempt at manipulative reduction of the fragments can then follow.

TREATMENT

The plan of procedure varies with the individual case, and must be guided by the nature of the injury, the associated trauma, and above all by the presence and degree of dyspnea, cyanosis, and subcutaneous emphysema. The primary consideration is the maintenance of an adequate airway, either through reconstruction of the normal passage or by the creation of a tracheotomy opening.

Aside from the surgical requirements to be met, two basic precautionary measures are incumbent upon the medical attendants. First, it must be remembered that, until either discharged as cured or safely decannulated, a patient with an injury to the laryngotracheal tract at any moment may develop an acute respiratory obstruction due to edema, mucus, blood clots, fragments of cartilage, and the like. Such a patient, although quite comfortable, might suddenly go into acute respiratory distress. Constant surveillance is imperative. Sudden dyspnea, stridor, or wheezing may require urgent bronchoscopy or tracheotomy. Second, the administration of narcotics in the presence of respiratory distress, cyanosis, or stridor is fraught with danger. It is important that no sedative or narcotic be given in the presence of obstructive dyspnea, for, by doing so, accessory respiratory efforts will be paralyzed. Despite accompanying restlessness and anxiety, it must be realized that any attendant dyspnea is compensatory, and that its alleviation by drugs will permit acute asphyxia and anoxia to go unrecognized until death suddenly occurs. Cyanosis cannot be used as an accurate indication of the degree of asphyxia, for it may not appear until just before death. The restlessness and respiratory distress should be relieved by the administration of oxygen and by the creation of an adequate airway, not by sedatives.

Associated subcutaneous emphysema is usually progressive and frequently demands surgical intervention. In cases in which it is not too severe, small incisions through the skin and subcutaneous tissues of the neck may be helpful by relieving the tension. This plan of treatment alone was successfully employed in one case of subcutaneous rupture of the trachea in our series. Suprasternal subcutaneous emphysema resulting from intrathoracic rupture of the trachea or bronchus demands prompt and adequate incision and drainage of this fossa with a large rubber tube so as to relieve the associated mediastinal emphysema.

The principles of treatment will be governed first by the degree of respiratory distress; second, by the character of the wound which may be small, large or intermediate; third, by its anatomical situation; and fourth, by the type of trauma.

A. Small wounds. With a small wound of the puncture type and with slight symptoms, i.e., in patients in whom there is an absence or minimum of dyspnea, cyanosis, subcutaneous emphysema, and bleeding, expectant treatment is indicated. As already stated and emphasized, supervision must be constant. With the advent of any respiratory difficulty, prompt intervention by bronchoscopy or tracheotomy will become necessary. Sedation is to be avoided, but if necessary, minimal dosage is to be prescribed.

B. Large wounds. The situation in such instances usually demands prompt surgical action.

Serious bleeding, which is frequently present, must be controlled. The divided air passages may be dealt with in a number of ways, governed by the nature of the injury and the attendant symptomatology. The procedures that may be used in dealing with the severed air passage are (1) primary suture without complementary tracheotomy; (2) primary suture with complementary tracheotomy; (3) introduction of a cannula into the tracheal wound; and (4) anchoring the distal end of a completely divided trachea into the wound.

Primary suture without complementary tracheotomy is indicated when the air passage has been lacerated by a sharp instrument, as in the ordinary case of cut throat. This procedure had been followed in 7 cases in our series without any subsequent complications. When there is respiratory distress with primary suture, or when such distress is anticipated because of associated edema, hemorrhage, or tissue trauma, complementary tracheotomy is indicated. Instead of performing a complementary tracheotomy, the operator may elect to introduce a tracheotomy tube into the wound in the air passage, with or without partial suture of such wound. Such a procedure would be governed by the nature of the wound and the urgency with which it must be completed. Occasionally, when there is complete division of the trachea, re-establishment of continuity may not be possible because of irreducible retraction of the divided ends. In such an instance, as a life-saving procedure, it will become necessary to anchor the distal end into the wound, preferably with a tracheotomy cannula in place. This was done in one of our cases, with recovery from the acute episode and subsequent discharge from the hospital. As is rarely the case, the distal end may retract behind the sternum, lending extreme difficulty to primary repair or to the introduction of a tracheotomy tube. In such a situation an improvised rubber tube cannula can be introduced and more satisfactorily retained in the distal end of the trachea.

C. Intermediate wounds. It is in the intermediate type—the wound in which it is evident that injury of the trachea or larynx is not too big and the patient presents no respiratory distress, no increasing subcutaneous emphysema, and but little bleeding—that the decision for or against surgical intervention always cannot be readily made. The potential danger of sudden acute asphyxiation must be borne in mind even when the situation appears to be under control. Richards, quoted by Remy-Néris, reported an instance of sudden fatal asphyxiation in a patient suffering from an asymptomatic bullet wound of the trachea. The advantage to both the patient and the surgeon of a tracheotomy performed without haste is self-evident. An attempt to execute the procedure under the duress of asphyxiation, a rapidly developing subcutaneous emphysema, or a pulmonary complication, may be very trying. The necessity for prophylactic tracheotomy should be seriously considered in instances in which respiratory obstruction may be anticipated, or in which careful and adequate observation cannot be rendered.

If the pharynx has been entered, as may be the case with wounds above the hyoid bone or through the thyrohyoid membrane, the edges of the pharyngeal mucous membrane should be carefully trimmed and reunited with interrupted chromic catgut sutures. A severely injured submaxillary gland can be removed.

Epiglottis. With wounds through the thyrohyoid membrane or above the hyoid bone, the epiglottis may be partially or completely divided. Repair of the epiglottis should be attempted using absorbable sutures. Sutures ordinarily hold well in this location. Bailey reports an instance in which a fragment of over an inch was removed without ill effect. Successful repair of a partial laceration of the epiglottis was done in one of our cases.

Lacerations of the esophagus. Lacerations of the esophagus must be carefully repaired, an adequate airway being assured in the interim. The technique of esophageal suture as described by Scott is a good one. In his case of complete division of the esophagus and trachea, a satisfactory suture repair was made. In uniting the esophagus, interrupted chromic catgut sutures are used, the posterior muscular coat being approximated first, and the posterior mucous membrane next, the knots being tied on the inside of the lumen. The anterior mucous membrane is then united, the knots being tied external to the lumen. Finally, the anterior muscular coat is sutured. This method was employed in the case of complete tracheo-esophageal laceration in our series. When found to be divided, the deep fascia and constrictor muscles should be reunited.

Gastrostomy. With associated injuries to the pharynx or esophagus, gastrostomy may become necessary in order to safeguard the suture line, to minimize the possibility of infection, and to insure adequate nutrition. Such a procedure may be done directly following the wound repair, or at any time during the postoperative course, should the indication arise. In the case in our series, it was performed on the 13th postoperative day because of feeding difficulties. As an alternative, a feeding tube may be passed through the nasopharynx into the stomach at the time of operation.

Suture of the trachea and thyroid cartilage. Lacerations of the thyroid cartilage and trachea are to be sutured whenever feasible. Cartilage, particularly the thyroid cartilage, is notoriously difficult to repair as the suture tends to cut through. Approximation can be successfully effected if the needle used is not too big, and if one uses mattress sutures which are not tied too tightly. The trachea lends less difficulty since the suture can be passed around the tracheal rings above and below the laceration. These sutures, preferably of fine chromic catgut, should be interrupted, and wherever possible should be tied on the outside. With complete division of the trachea, it is obvious that the sutures uniting the posterior wall must be tied on the inside of the lumen. Careful approximation is required to

avoid complicating subcutaneous emphysema or local infection. With separation of the tracheal ends following complete division or rupture, approximation and suture may be performed if this separation does not exceed 2 to 4 centimeters. Beyond this limit of separation the suture line is apt to give way (Gluck, Nowakowsky). If the strength of the suture line is in doubt, the latter can be reinforced by a pedicle muscle flap taken from the sternomastoid or ribbon muscles. Such reinforcement will help protect the overlying tissues against complicating infection or subcutaneous emphysema.

Repair of defects with fascial transplants. Relative to the repair of laryngotracheal defects, the experimental work of Taffel is suggestively promising in its clinical application. This worker was able to effect an airtight repair of resected full-thickness segments of the trachea and bronchus in dogs by means of free fascial grafts. Such fascial grafts provided immediate restoration of the airway, thus preventing any leakage of air or secretions. As in other sites these fascial transplants undergo connective tissue replacement, the latter remaining as a permanent supporting structure firmly covering the defect. As described by Taffel, "the new and final structures which served to restore the continuity of the viscus were composed of (1) an inner layer of pseudostratified epithelium; (2) a layer of submucosa with occasional mucous glands and a few small islands of new cartilage, but with occasional exceptions, no fibers of muscularis mucosa; and (3) an outer layer of supporting adult connective tissue." This procedure possesses potential clinical application in instances in which loss of a considerable amount of substance from the laryngotracheal tract has occurred. Fascia in amount adequate for such purpose is readily obtainable from the region of the neck wound as well as from the customary source in the thigh.

Use of the sulfonamides. Because of their proved value in traumatic wounds, and because of the seriousness of suppuration in the deep layers of the neck, these potentially infected wounds involving the air passages and esophagus should be treated by the routine implantation of the sulfonamides into the adjacent tissues. Supplementary oral or parenteral administration of these drugs may be necessary.

Tracheotomy. It must be emphasized that tracheotomy, when indicated, should be done early and not hurriedly. When delayed and hastily performed, the procedure may be trying to the surgeon and dangerous to the patient. The distinction between high and low tracheotomy in relation to the thyroid isthmus is no longer of great importance since surgeons have learned how to divide this structure quickly and safely. The method of dividing the thyroid isthmus as described by Digby is most helpful. Controversy between the use of laryngotomy and tracheotomy still exists. The English surgeons have commonly practiced laryngotomy for wounds above the level of the cricoid cartilage, inserting the laryngotomy tube through the cricothyroid membrane. Laryngologists in this country, particularly Chevalier Jackson, have decried high tracheotomy because of the frequency of ultimate perichondritis and laryngeal stenosis. In our series all tracheotomies performed were of the low type. There were no immediate tracheotomy complications. Because of the difficulty of follow-up in these patients, it is impossible to state whether there were any delayed sequelae.

Anesthesia. Local anesthesia is by far the safest. Under such conditions, general anesthesia is dangerous; it abolishes the action of the accessory muscles of respiration, the function of which is so important in the presence of obstructive dyspnea. If a general anesthesia is required, as in the case of a child, it is most safely administered through a bronchoscope.

Position of the patient. This is an important detail. The patient is restrained on the table in the appropriate manner. A sandbag or rolled up sheet is placed underneath the patient's shoulders —not underneath the neck. The head is then fully extended so that the chin and sternal notch are in the same straight line (Fig. 3). An assistant placed to the left of the patient's head is designated to immobilize the head in this position by placing the right hand over the frontoparietal region and the left hand under the occiput.

Technique of tracheotomy. An adequate midline incision is made from the thyroid notch to the suprasternal notch. The cricoid is identified and the dissection is continued in depth below this point. The prethyroid muscles are separated in the midline, thus exposing the trachea and thyroid isthmus. The isthmus can be retracted upward if not too large, but if it overlies the site of the tracheotomy, it is safer to divide it. Avoidable mortalities have occurred because of the slipping of a large undivided thyroid isthmus back over the tracheotomy opening during the early postoperative period when the cannula has either been removed for cleansing purposes or has slipped out. Division of the thyroid isthmus is best accomplished in the manner described by Digby. A transverse incision is made in the fascia at the lower border of the cricoid, thus exposing the trachea above the thyroid isthmus. A curved hemostat passed posterior to the isthmus from above downward bluntly separates the latter from the trachea, the hemostat being opened and closed to

facilitate its passage. The isthmus which is clamped by two parallelly placed hemostats is then divided. The isthmus is freed further from the trachea by externally rotating the hemostats, at the same time slightly depressing the handles so as to elevate the points. Supplementary sharp dissection may be necessary. Conditions permitting, all hemostasis should be effected before the trachea is opened. The cricoid is steadied by means of a sharp hook which is pulled in an upward direction. The trachea is opened by a vertical midline incision through the 3rd, 4th, and 5th rings. The knife is held in the manner of a pen with the sharp edge directed anteriorly, so as to avoid laceration of the posterior wall of the trachea. The tracheal opening is gently separated with a Trousseau dilator or a hemostat and a cannula is inserted. Instead, one can make an oval window in the trachea just large enough to admit a cannula.

For a "tranquil tracheotomy," Thompson advises the intratracheal instillation of 20 drops of 2 per cent cocaine through a hypodermic syringe. The liquid thus introduced into the trachea may cause a slight cough but no distress. After 10 minutes, if conditions permit, the trachea can be opened and the tracheotomy tube introduced without any cough or spasm.

In the choice of a tracheotomy cannula, adequate length is important. Too short a cannula may slip out of or be pulled from the trachea by careless handling or by postoperative soft tissue swelling, with resultant asphyxia.

The skin about the tracheotomy cannula should not be sutured too closely. This might cause a retention pocket for the tracheobronchial secretions which pass out alongside of the tube, with the danger of complicating local infection.

Emergency tracheotomy. When asphyxiation is acute, promptness and speed of action may be life-saving measures. The details of technique just described may of necessity be waved aside. If cyanosis is marked and breathing has ceased, one may not countenance any delay, not even for local anesthesia. The procedure should be rapidly executed, but with care and precision. The head is fully extended as described. The operator, standing to the patient's right, places the thumb and middle finger of his left hand on either side of the trachea, making sustained pressure posteriorly and laterally against the sternomastoid muscles and the underlying carotid sheaths. This throws the trachea into prominence. An adequate midline incision is made from the thyroid notch to the suprasternal notch. Suction, when available, will help to keep the operative field free of blood. With the thumb and middle finger in position, the left index finger is passed along the left side of the trachea. The scalpel is placed medial to the index finger so that the 3rd, 4th, and 5th tracheal rings are incised in the midline. Despite the haste and free bleeding, care should be exercised to avoid cutting the cricoid or thyroid cartilages or the posterior wall of the trachea. The tracheal wound, held open by a Trousseau dilator or hemostat, is then cannulated. The head is lowered and turned to one side so as to permit the blood to run away from the tracheal wound. If breathing has ceased, artificial respiration should be given and oxygen passed through the cannula, but not too forcibly. Hemostasis is then effected. When the ordinary tracheal cannula is not available, or should it be too short, one can be improvised from a piece of firm rubber tubing, reaching, if necessary, to the bifurcation of the trachea.

Complications. The literature appears to be indefinite concerning the immediate complications. Jackson and Jackson state that bronchopneumonia is infrequent, whereas Bailey cites the frequency of this complication. In our series there were no immediate pulmonary sequelae. Four of the patients developed wound infections which were readily controlled by local treatment. Since these patients have been treated on an acute traumatic surgical service, we are not in a position to report on the delayed complications such as stricture or perichondritis. Moreover, any such complications would come to the attention of the laryngologist. Remy-Néris mentions the apparently greater incidence of pulmonary tuberculosis following injury to the laryngotracheal tract. We are in no position to comment upon this inference.

ANALYSIS OF CASES

In our series there were 17 cases of injury to the larynx and trachea. Three of these were subcutaneous ruptures of the trachea. Of the remainder, 13 were the result of lacerations and one was caused by a gunshot. All patients were admitted to the hospital within 3 hours following injury. The mortality rate was 5.8 per cent for the entire series. The one patient who died was admitted in shock with an associated laceration of both external jugular veins. Shock was never relieved and death occurred on the operating room table.

In 7 cases, immediate primary repair of the tracheal wound was performed without complementary tracheotomy. One patient had a tracheotomy tube inserted into the original wound. Because of further bleeding and dyspnea in this case, the tracheal wound was repaired within 4 hours

ANALYSIS OF CASES

	Initial	Color	Age	Sex	Weapon	Injury	Associated injury	Procedure	Course	Stay in hospital
1.	N.	T.	30	M	Knife	Thyroid cartilage	Laceration of submaxillary gland	Immediate repair	Uneventful	Signed out 2 days
2.	N.	S.	30	M	Knife	Thyroid cartilage	Shock, multiple lacerations	Immediate repair	Uneventful	13 days
3.	H.	W.	26	M	Knife	Thyrocricoid membrane	Stab wound of chest with pneumothorax, shock	Tracheotomy tube into original wound, primary repair	Uneventful	18 days
4.	F.	M.	31	M	Knife	Thyroid cartilage	Shock	Immediate repair	Infected	17 days
5.	P.	T.	27	M	Knife	Trachea		Immediate repair	Uneventful	8 days
6.	J.	Q.	36	M	Knife	Thyrohyoid membrane. Pharynx exposed. Partial division of epiglottis	Shock, lacerations of chest and wrist	Repair of laceration and epiglottis, low tracheotomy	Uneventful	12 days
7.	C.	N.	20	M	Gunshot	Trachea	Anterior jugulars	Immediate repair	Infected	24 days
8.	C.	W.	29	M	Knife	Complete division through thyrocricoid membrane	Complete division of esophagus	Esophagus reconstructed. Posterior trachea closed. Tracheotomy tube into anterior opening	Gastrostomy on 13th day	46 days
9.	S.	M.	39	M	Knife	Trachea	Multiple lacerations	Unable to close trachea. Packed	Uneventful	12 days
10.	A.	M.	29	M	Knife	Trachea		Immediate repair	Uneventful	11 days
11.	W.	H.	54	M	Knife	Trachea		Tracheotomy into original wound because of bleeding, reoperated upon in 4 hrs. and trachea repaired. No tracheotomy	Uneventful	14 days
12.	L.	P.	42	M	Knife	Trachea	External jugulars, shock	Immediate repair	Died of shock on table—4 hrs.	
13.	L.	H.	49	M	Knife	Trachea	Amputation of penis	Immediate repair of trachea	Uneventful	14 days
14.	N.	G.	38	M	Knife	Trachea	Penetrating stab wound of chest with pneumothorax	Tracheotomy into original wound	Uneventful	15 days
15.	H.	M.	55	F	Auto accident	Subcutaneous rupture of trachea		Conservative until tracheotomy on 4th day	Infected	Signed out 13 days
16.	I.	M.	31	F	Kicked	Subcutaneous rupture of trachea	Incision of soft parts to relieve subcutaneous emphysema, no repair		Infected	17 days
17.	W.	B.	25	M	Kicked	Subcutaneous rupture of trachea		Conservative	Uneventful	6 days

without complementary tracheotomy. In another instance, the divided tracheal ends were too far apart to permit accurate approximation. The peritracheal tissues were packed without tracheotomy. One patient had the original wound closed and a low tracheotomy tube inserted. In the patient with the combined esophagus and trachea injury, after reconstruction of the esophagus and posterior trachea, a tracheotomy cannula was inserted into the anterior portion of the tracheal opening. This patient also required a gastrostomy on the 13th day. In 1 case the laceration extended through the thyrohyoid membrane into the pharynx with partial division of the epiglottis. In 5 patients a tracheotomy tube was inserted into the original traumatic opening.

Of the 3 cases of subcutaneous rupture, one patient was treated conservatively. Another was

treated conservatively until marked dyspnea resulted on the 4th day when an emergency tracheotomy was performed. In the third case, small puncture wounds were made in the skin of the neck to relieve the subcutaneous emphysema.

All operative procedures were carried out under local anesthesia, except in one case in which intravenous evipal was used. Five patients were admitted in shock, one of whom never recovered. Two patients developed a tension pneumothorax from associated stab wounds of the chest. There were no other pulmonary complications. Complicating wound infection occurred in four instances. The average stay in the hospital for all types of cases was 18 days.

SUMMARY

1. The results of a study of trauma to the laryngotracheal tract are offered from the perspective of the general surgeon rather than that of the laryngologist. Consideration has been given to instances of subcutaneous rupture as well as those due to direct trauma.

2. Successful results, particularly with the subcutaneous rupture type, are contingent upon early recognition and the institution of appropriate treatment.

3. The necessity for the maintenance of an adequate airway, either by operative repair, tracheotomy, or bronchoscopy has been stressed.

4. The potential danger of asphyxia by the careless use of sedatives has been emphasized.

5. The appropriate types of treatment have been considered.

6. The technique for the elective and the emergency types of tracheotomy have been described in detail.

7. The various complications have been considered.

8. The mortality rate in our series was 1 case in 17, or 5.8 per cent. This 1 death appears to have been due to hemorrhage and shock rather than the injury to the trachea *per se*. The remainder of the patients were successfully handled by various forms of treatment rendered in accordance with the nature of the injury and the presenting symptoms.

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EXPERIMENTAL HEAD INJURY WITH SPECIAL REFERENCE TO THE MECHANICAL FACTORS IN ACUTE TRAUMA

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THE view has been presented that the effects of cranial trauma are more profound to the nonfixed than to the fixed head. Experimental data have been submitted to show that injury of a critical velocity suddenly setting the head into motion may produce unconsciousness (concussion) and even death (6). Under these circumstances, pathological changes in the brain were absent or, if present, were considered to be incidental.

In our experience, the physiological effects observed in patients with head injury have seemed, in general, to correlate with the intensity of the injuring force and the pathological changes produced in the brain. In order more clearly to understand the mechanics of injury as related to the physiological and pathological effects, experiments were performed upon 150 dogs by varying the type and intensity of the injury to the fixed and nonfixed head.

METHOD AND PROCEDURE

Mongrel dogs with an average weight of 8.51 ± 2.87 kilograms were used for the study. Morphine in quantities of 20 milligrams per kilogram was the anesthetic used in the experiments. Before injury, the scalp and masseter muscle were infiltrated with 1 per cent procaine solution and then reflected from the bone. The striking objects made direct contact with the parieto-occipital bone. The blood pressure was recorded from the femoral artery; respirations, by means of a balloon about the thorax. The spinal fluid pressure was recorded from a needle inserted into the cistern and attached to a 1 millimeter bore water manometer. Six-tenths cubic centimeter of cerebrospinal fluid was required to fill the system to starting pressure. The corneal and palpebral reflexes were evaluated by appropriate stimuli before and after injury. The state of consciousness was determined by the animal's response to tail and paw pressure stimuli. The morphinized animal would react to from 4 to 8 kilograms of tail pressure; the unconscious animal showed no response to stimuli. Differing from the effects of barbital or ether anesthetics, morphine clearly permitted recognition of unconsciousness.

Various mechanical devices were used to produce the injuries. These are shown in Figure 1. Injury to the fixed head was accomplished by a directed falling weight of 5.5 pounds and by hammer blows. The nonfixed head was struck by means of a hammer; by a hitting object propelled by a pendulum and also by a spring. High ranges of velocity were produced by the pendulum, the axis of which was eccentric serving to rotate 140 pounds of weight. The spring device was similarly able to develop high velocities by virtue of the type and position of the spring. Penetrating injuries were produced with gunshot and a mechanical drill. Twenty-two caliber bullets of varying velocity and size were employed. A mechanical drill was used to obtain a penetrating injury of minimal velocity. In a number of instances, gunshot wounds were made after disturbance of the closed cavity hydrodynamics by opening the cistern to expose the medulla; suboccipital craniectomy and unilateral or bilateral craniectomy to expose one or both hemispheres. Infiltration of 1 per cent procaine was used in these procedures for local anesthesia.

DISCUSSION OF EXPERIMENTAL DATA

The injuries produced in this study were divided into three groups. The first group included animals injured by a falling weight or hammer blow striking the fixed head (30 experiments). The second group was comprised of animals which were struck by objects of graduated velocities applied to the nonfixed head. The origins of these forces were the hammer (26 experiments), pendulum (24 experiments), and the spring (20 experiments). The third group sustained injuries of a penetrating type including gunshot injuries (38 experiments).

The acute physiological effects and the pathological damage under these varying conditions were studied and correlated. Particular concern

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was given to the state of consciousness, the corneal and palpebral reflexes, the respiration, the blood pressure, the intracranial dynamics, extensor phenomena, the convulsive state, the morbidity, and the mortality. The resultant skull and cerebral injuries were classified according to the degree of changes produced.

Three levels of the physiological response to the cranial trauma were seen. These were :(1) minimal; (2) moderate; (3) profound. The animals in the minimal group tolerated the injury with no significant changes in the vital functions of respiration, blood pressure, and reflexes. Animals in this group uniformly survived the acute injury. The moderate group included animals in which there occurred a cessation of the respirations or an interruption of the corneal and palpebral reflexes. A temporary rise in blood pressure was usually observed. The animals lost consciousness for variable periods of time. Animals in the moderate group were not all able to survive the injury. The profound group was characterized by the death of the animal during the acute experiment. Respirations and the corneal and lid reflexes were usually abolished. A remarkable temporary rise in blood pressure with tachycardia was a characteristic reaction. The animal was unconscious until its death.

The pathological damage to the brain could be classified into four groups irrespective of the mechanism of injury. These were: group 1, no gross lesion but occasional slight congestion; group 2, cerebral contusions, grade 1 and 2; group 3, cerebral contusions, grade 3 and 4; group 4, brain laceration and contusions. The skull was fractured in all instances except when indicated in the various charts.

Forces of varying intensity applied to either a fixed or nonfixed head were observed to produce physiological responses proportional to the degree of pathological damage to the brain. The attempt to produce profound physiological effects without producing pathological damage failed. The results of the injuries are illustrated in charts and described and discussed under subject heading.

THE CONSCIOUS STATE

An evaluation of the conscious state was made before and after each injury. The usual morphinized dog was conscious before the injury occurred. Although this state was depressed, the animal could still respond to external stimuli of sensitive regions. Tail pressure was administered with a dynamometer and the level of response was recorded. Further depression or complete failure of response after the injury could be evaluated.

An attempt was made to produce unconsciousness without associated gross pathological change in the brain (concussion) since this is an interesting and controversial subject. It was possible to do this in but a few instances. In order to produce loss of consciousness, it was necessary, as a rule, to produce cerebral contusions. The striking forces were varied in the attempt to produce not only concussion but concussion with resultant death of the animal. As shown in charts, Figures, 2, 3, and 4, fatalities resulted only after injuries which were severe enough to produce high grades of pathological damage. Death from concussion did not occur.

Brief periods of unconsciousness and semiconsciousness were observed in the minimal groupings. Depression of the conscious state was the commonest finding. In the moderate group, consciousness was frequently lost for prolonged periods. In the profound class, the unconsciousness was uniformly followed by death.

The relationship of the conscious state after injury to the corneal and palpebral reflexes was studied. Analysis showed that a number of conditions were possible. Loss of consciousness frequently obtained with no changes in the reflexes. Loss of consciousness and loss of reflexes were frequently found together; in some instances the reflexes would then return while the animal continued in an unconscious state. A consistent finding without exception was that consciousness was never present during the period of reflex loss. The observations made it clear that loss of consciousness and loss of the corneal and palpebral reflexes did not represent the same level of response to injury.

RESPIRATIONS

The effects of cranial trauma were found to be intimately associated with the mechanism of respiration. In some instances pathological damage to the brain was produced without recordable evidence of any influence upon the respiratory activity. Application of forces producing moderate physiological effects usually resulted in cessation of respiratory function for variable periods of time. In a few instances the respirations were stimulated. The time interval of respiratory loss until recovery varied from a few seconds or a respiratory pause to losses for as long as 200 seconds. The cessation of this function was usually attended by an absence of the corneal and palpebral reflexes and unconsciousness. In the profound group, respirations were abolished completely and usually permanently. This was not a uniform finding permitting the conclusion that the respiratory centers were more vulnerable than

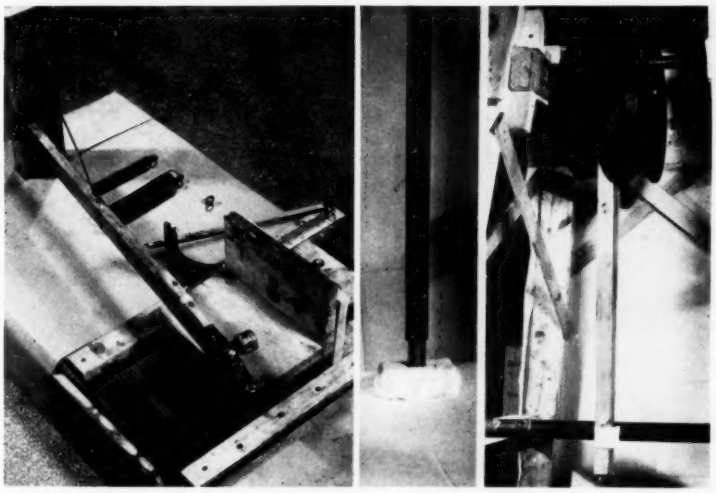

Fig. 1. The devices used to injure the head, showing from left to right, the spring instrument, the falling weight, and the pendulum.

other vital centers; that death occurs because the respiratory centers have ceased to function. Evidence to the contrary was found in the observation made a number of times that the respiratory activity returned but that the heart continued to fail in spite of renewed oxygenation. In other cases of temporary recovery of the respiratory centers, the onset of oxygen intake in the presence of a failing blood pressure was immediately revivifying. Rises and falls in the blood pressure then occurred synchronously with each respiration. Comparison of the vulnerability of the respiratory and reflex centers to trauma showed a wide variation in the response of each, illustrated best among the injuries in the moderate group. Absence of respiration for an interval comparable to the period of loss of the corneal and lid reflexes was commonly observed. Also frequent was abolition of the eye reflexes with no changes in the respiratory activity. In some instances the reflexes were lost for longer periods than the respirations.

REFLEXES

The activity of the lid and corneal reflexes mediated by the 5th and 7th cranial nerves offered a valuable index of severity of injury. In this respect, the minimal group were characterized by no changes in activity. In the moderate class, these reflexes were lost for periods which varied from a few seconds to 6½ minutes. Injuries resulting in a profound response were attended usually by loss of activity to the animal's death. In a few instances there was a temporary recovery of function with secondary loss of activity. In our experience, loss of the lid and corneal reflexes represents a more profound response to trauma than unconsciousness.

The reflex of deglutition was found to react in the manner of other bulbar reflexes. Particular attention was given to this reflex in relationship to the unconscious states produced. It was noted that this reflex as well as the corneal and palpebral were frequently preserved in unconscious animals. Hopping and stepping reflexes were lost during unconsciousness. Deep tendon reflexes remained.

BLOOD PRESSURE

A remarkable rise in blood pressure was usually observed after injuries in the moderate and in the profound classifications. The rise was prompt and reached levels of 300 millimeters of mercury. Tachycardia always accompanied the rise in pressure. In the moderate group, the maximum rise would be maintained over 60 to 120 seconds. In the profound group, the pressor effect continued usually through a period of 180 seconds and gradually failed to zero at the animal's death. There were some instances among the more severe injuries in which hypertension did not occur. It was notably absent when a crushing injury to the skull and brain was produced; in this circumstance, an immediate fall in pressure was sometimes noted. Strong vagal influences were frequently observed to interrupt the tachycardia.

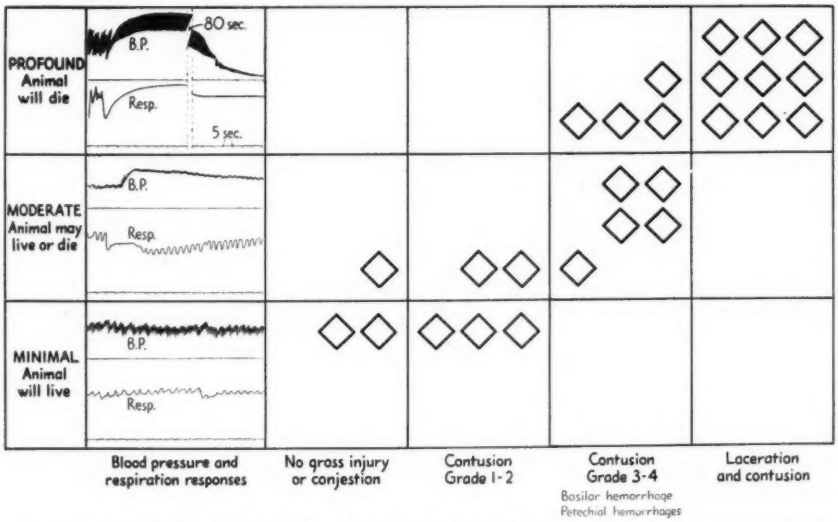

Fig. 2. Correlation of the physiological and pathological effects of injury to the fixed head. Profound effects did not occur unless gross damage was produced. ◇ Indicates falling body.

Study directed at defining the mechanism responsible for the hypertension showed that it could be prevented from occurring by section of the spinal cord at the first thoracic segment. These animals were prepared the day before injury and were then subjected to blows which resulted in profound effects without hypertension. Removal of both adrenal glands had no effect upon the pressor response after injury. Yohimbinized animals, which did not respond to adrenalin, showed no rise in pressure following injuries of fatal intensity. The observations which we have made favor the conclusion that the activity of the sympathetic nervous system is the cause for the acute hypertension resulting from injury to the head. Measurement of the blood flow in the spleen and in the hind paw showed a decrease in flow in the splanchnic distribution and increased blood flow in the hind paw. A similar dissociation of the blood flow in the splanchnic and peripheral circulations has been observed by Green and Hoff following stimulation of the cerebral cortex. Gunshot injuries, discussed under a separate heading, were of particular interest in respect to the occurrence of hypertension at the time of injury. These injuries produced a uniform pressor effect similar to that noted in the low velocity nonpenetrating types of injuries. The hypertension could be prevented from occurring by a bilateral decompression of bone and dura mater. Injury to the medulla also resulted in absence of the pressor response.

The question may arise as to the rôle of the cortex in mediating or assisting in the pressor response. A remarkable rise in blood pressure after cortical stimulation has been recorded by Green and Hoff and Crouch and Thompson. Stimulation of the hypothalamus may also result in hypertension (7). The significance and rôle of the lower brain stem centers, however, have been clearly defined by Denny-Brown and Russell who showed that the pressor response occurred in head injury after decerebration of the animal preparatory to injury.

INTRACRANIAL HYDRODYNAMICS

The spinal fluid pressure, in most cases, was measured shortly after the production of the injury. A pressure was recorded usually in the range of between 100 and 200 millimeters of water. (The highest pressure observed was 300 mm.) These findings were similar to those previously reported (26). Others have also found but a small rise in the cerebrospinal fluid pressure after injury of the experimental animal (6) and no significant change in the water content of the brain (20).

Blood was commonly noted in the spinal fluid. The degree of bloodiness was commensurate with the intensity of the injury in most cases. Increasing quantities of blood in the fluid were associated with correspondingly higher pressures, results being similar to those reported in detail (26).

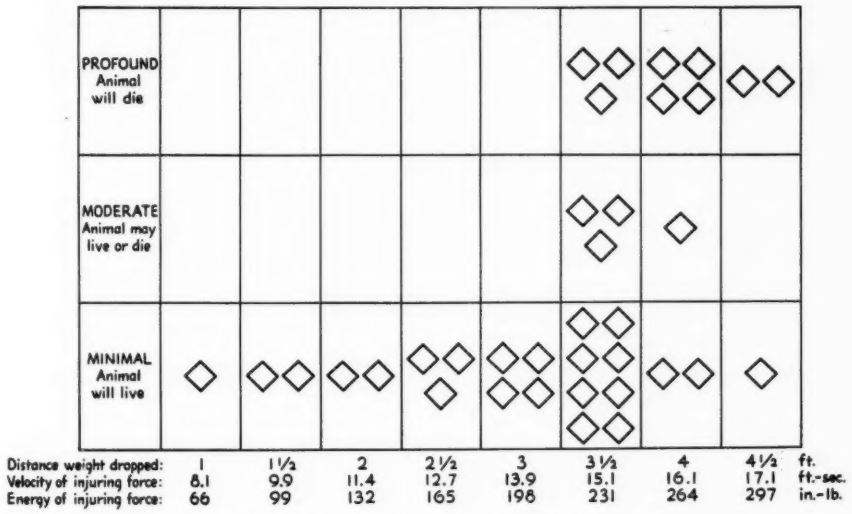
PROFOUND
Animal will die
MODERATE
Animal may live or die
MINIMAL
Animal will live
Distance weight dropped: 1 1½ 2 2½ 3 3½ 4 4½ ft.
Velocity of injuring force: 8.1 9.9 11.4 12.7 13.9 15.1 16.1 17.1 ft.-sec.
Energy of injuring force: 66 99 132 165 198 231 264 297 in.-lb.

Fig. 3. Correlation of the velocity and energy of the injuries (5.5 pound weight) to the fixed head with the physiological effects. ◇, Falling body.

Injuries produced by gunshot wounds gave evidence of an intense increased intracranial pressure at the instant of injury. Such a pressure effect was visualized by exposure of the cisterna magna; at the moment of injury the cerebellum was extruded into the opening. A suboccipital craniectomy followed by a supratentorial, gunshot wound was observed to result in expulsion of the cerebellum with such force as to lacerate that tissue. A gunshot injury striking 5 centimeters below the medulla and transecting the cord resulted in cerebral contusions of the cortex of the hemispheres due possibly to transmitted high pressure. Cerebral tissue was consistently extruded through the defect made by a bullet's entrance. Measurement of the intracranial pressure at the time of injury by means of a fluid system, attached by copper tubing to a tambour from an adapter screwed into the skull, showed this instant qualitative change in pressure.

PATHOLOGY

The pathological findings were grouped according to the degree of injury to the brain and skull as previously noted. Brain injury was absent or there was congestion at the site of injury, in the animals of group 1; mild contusions graded 1 and 2 were present in group 2; severe bruising graded as 3 and 4 was present in group 3; brain laceration and contusion were characteristic findings in group 4. Similarly the degree of bone deformation was graded. A fine fracture was present in grade 1; linear but more extensive fracture in grade 2, depressed in grade 3 and comminuted and depressed in grade 4.

Group I. The animals in this class showed no cortical damage. Congestion of the surface vessels at the point of injury sometimes occurred. Congestion was defined as present when the vessels were merely more prominent than in the normal brain. Cross sections of the brains showed no gross damage. Frequently a blanching of the bone was noted at the point of injury. In most cases a fine fracture occurred which was classified as grade 1. The injuries of this group occurred by the application of forces of the lowest intensity in the range used.

Group II. The second group of pathological specimens were characterized by mild degrees of contusions which were labeled as contusions grades 1 and 2. Contusions were usually found at the site of injury. Frequently they were located over the temporosphenoidal lobe and on the tentorial surface of the occipital lobes. They were sometimes present opposite to the point of impact under conditions of both the fixed and nonfixed head. Cross sections of the brains of the animals in this group, as a rule, showed no microscopic changes. A grade 1 or 2 fracture of the skull was usually present. In some instances, contusions grades 1 and 2 were observed without an associated fracture of the skull. This degree of bruising was

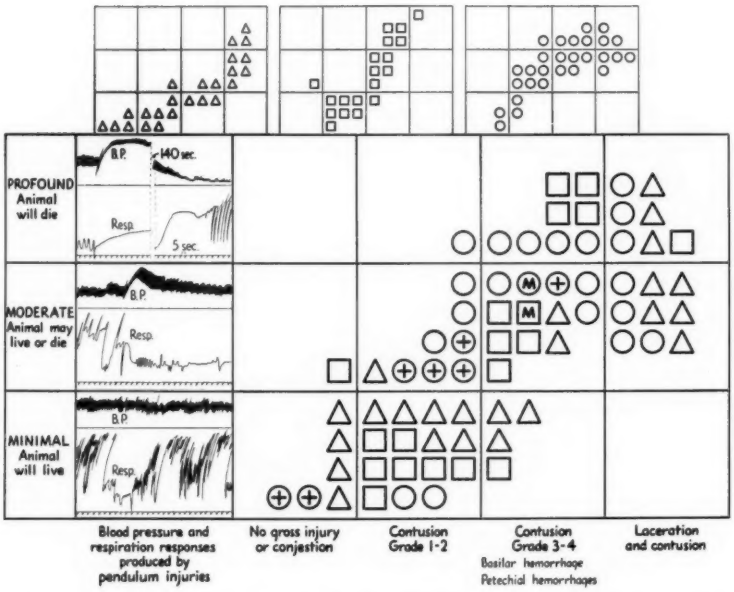

Fig. 4. Correlation of the physiological and pathological effect of injury to the nonfixed head by the pendulum, △, spring, □; and hammer, ○, showing a composite distribution and the distribution for each type of injury. Profound effects did not occur unless gross damage was produced. ⊕, Indicates no fracture; Ⓜ, multiple injury.

often found in the absence of any significant change in the animal's neurological status.

Group III. The third group comprised specimens which showed a greater area and depth of involvement by bruising. These contusions were graded as 3 and 4. There was frequently subdural and subarachnoid bleeding accompanying the more severe contusions. In some cases the specimens showed diffuse basilar hemorrhage which extended along the base to the spinal cord. Cross sections frequently revealed petechial hemorrhages in the brain stem. These were more commonly found in the presence of the diffuse basilar hemorrhage. The pons was the commonest site although the petechiae were sometimes noted in the cervical portion of the spinal cord and in the medulla. A fracture of the skull occurred in all the cases. Trauma which was severe enough to produce this degree of bruising, without exception, fractured the bone. The grades of fracture varied from grade 1 to grade 3. A grade 3 fracture is shown in the pathological chart.

Group IV. Brain laceration and contusion represented a fourth group including those specimens which showed the maximum degree of injury. Lacerations were always present although of varying severity; the local damage was prominent. The associated contusions were usually of grade 3 and 4. In all but a few instances, petechial hemorrhages were found upon cross section. These were usually more numerous and of wider distribution than similar lesions in group 3. Subdural, subarachnoid, and subpial hemorrhages were often marked. The bony injury in this group was characterized by extensive fracture and maximum deformity, classed as grade 4.

In the animals, it is notable that fracture occurred in most instances. In order to produce profound and moderate effects, it was necessary to deliver a quantity of energy which resulted in local injury and fracture of the skull. In humans, it is common to have severe pathological and physiological damage without an associated fracture. This fact represents an important animal-human difference present under the conditions of these experiments.

GUNSHOT INJURIES

Sir Victor Horsley observed the physiological effects of gunshot wounds of the brain in the experimental animal. Certain experiments dealt with the effects upon blood pressure and respira-

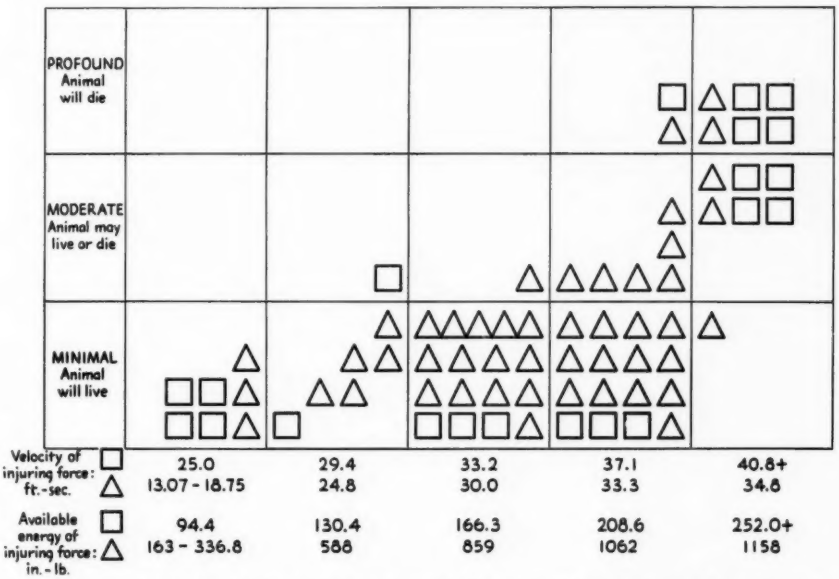

Fig. 5. Correlation of the velocity and available energy with the effects of injury to the nonfixed head. The animal's head was able to absorb the energy produced by the spring, □. With the pendulum device, △, much of the energy was expended into the stop bar after the head was set in motion.

tion. Kramer and Horsley (16) reported that death "is not, as usually supposed, due to failure of the heart, but to arrest of the respiratory movements." The changes in circulation consisted of "(a) slight initial fall of blood pressure, (b) considerable later rise of blood pressure, (c) preservation of the rhythm of the heart."

The observations which we have made confirm those of Kramer and Horsley concerning the importance and vulnerability of the respiratory center in gunshot wounds of the brain. The response of the vasomotor center to this type of trauma was found to differ from that reported by these observers. In our experience, the rise in blood pressure was abrupt, profound, and uniform in the high velocity group of injuries. The rise began at the moment of injury, it was not preceded by a fall in pressure. There was an associated tachycardia and increased pulse pressure.

The lid and corneal reflexes were deranged in direct proportion to the severity of brain stem injury, as were the respirations and vasomotor activity. In the profound group, these reflexes and the respirations were abolished. In the minimal group, although minor disturbances of respiratory rate occurred, reflex function was normal to all appearances. Unpredictable reactions of the vital mechanisms were observed in the moderate group. In some instances, respiratory activity alone was lost, the lid reflexes remaining active; in others, reflexes only were lost. In the largest group, both respiratory and reflex function were lost together and each recovered at varying and different periods. The absence of the lid and corneal reflexes was always associated with unconsciousness. However, unconsciousness was also found to occur in the presence of active lid and corneal reflexes. These phenomena were therefore similar to those observed after other forms of injury.

EVALUATION

Variations in the methods used to study head injury may account for the differing results and consequent conflicting viewpoints. The dog, cat, and rabbit have been mainly used in experiments on cranial trauma. The type of the animal, its age, the thickness of the bone of the skull, and the thickness of the masseter muscle are factors which can influence the responses to injury. In the dog, the masseter muscle, because of its development and attachment to the bone, provides a helmet-like protection. It is generally accepted that it is difficult to injure the dog fatally by means of blows to the head possibly due to muscle buffering

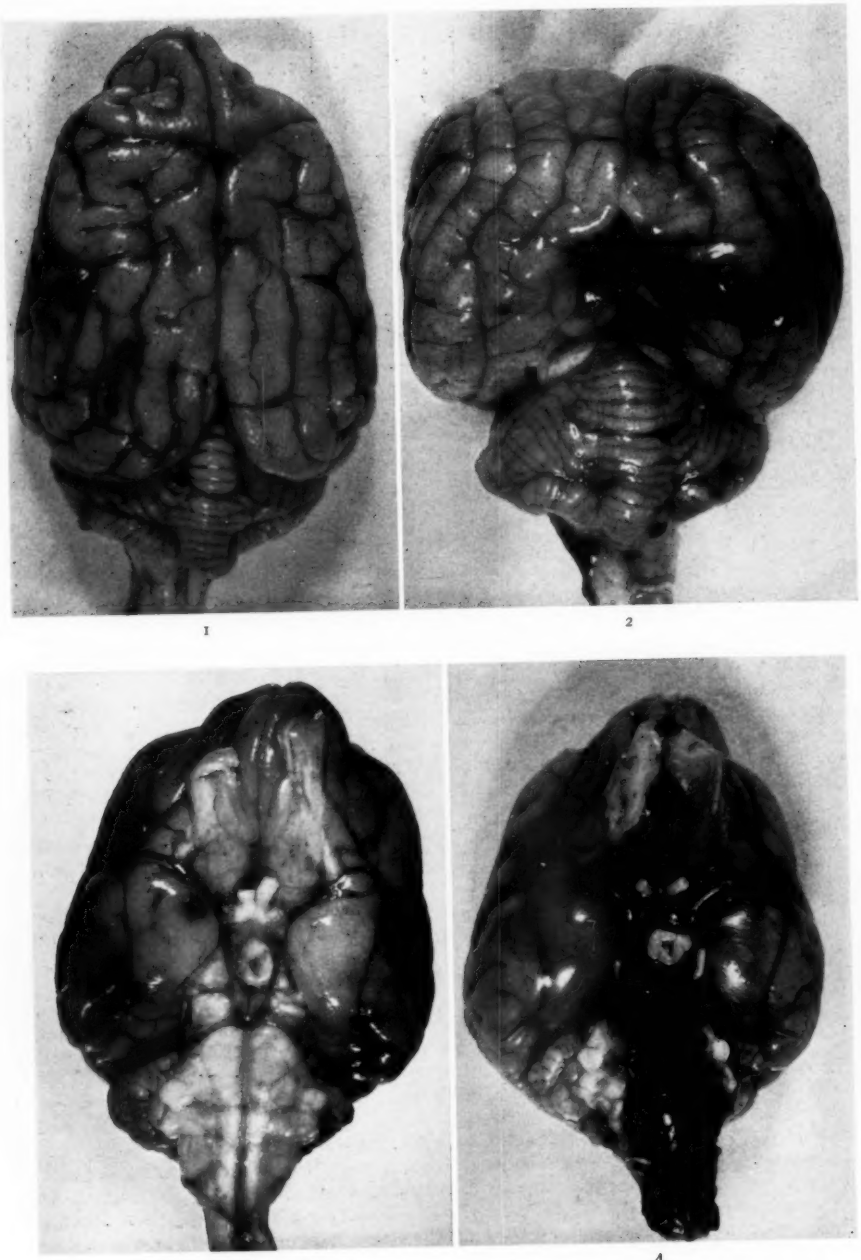

Fig. 6. Specimens illustrate the various degrees of pathological injury produced. Cerebral contusions were graded into 4 groups as indicated by illustration 1, 2, 3, and 4.

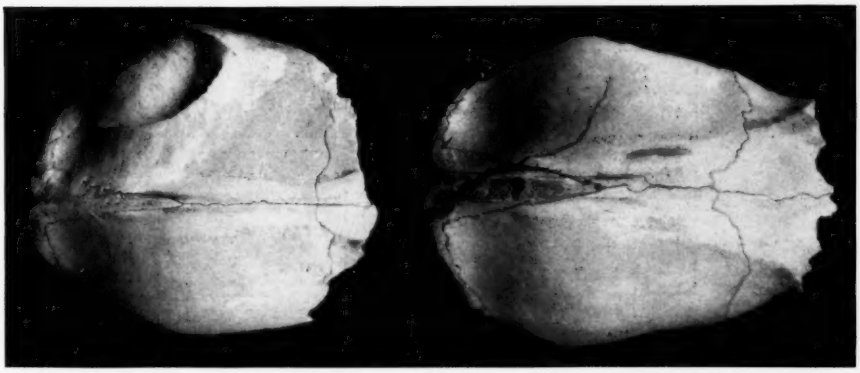

Fig. 7. Examples of fracture of the skull grade 1, left, and grade 3 are shown.

(1). Injury to the exposed skull or to the muscle protected skull may produce different effects. Various anesthetic agents have been used during the experiments, barbituric acid derivatives and ether being the most common. The effect of the anesthesia in its relation to the experimental results has not been critically analyzed. Such factors may account for the differences of opinions concerning the results of injury.

In the experiments upon dogs reported in this paper, an attempt was made to evaluate, as far as possible, the injuries under controlled conditions. For this reason, the selection of the type of anesthetic was held to be of first importance. Morphine analgesia was used since the state of consciousness could be readily recognized. Morphine does not influence the activity of the palpebral and corneal reflexes as may occur by the use of barbituric acid derivatives. In further interest of controlling the conditions of experiment, the site of injury was exposed in each instance to eliminate masseter muscle buffering. The variations in bone thickness and tensile strength could not be controlled. Measurements of the bone showed variations between $\frac{1}{32}$ and $\frac{1}{8}$ inch. Under these conditions the energies produced by the various striking devices usually resulted in predictable physiological and pathological responses. In the experiments, a correlation of the physiological and pathological changes was found to exist. Minimal, moderate, and profound physiological effects were associated with very slight, moderate, and severe pathological changes in the brain. That is, animals which were struck with sufficient force to produce changes in vital functions showed also gross pathological damage in the brain. If the force applied was insufficient to produce observable pathological changes, there were then no significant effects noted in the reflexes, the respirations, or in the blood pressure. Both physiological and pathological effects were found to be proportional to the intensity of the injuring force which was allowed to strike the head, irrespective of whether the head was fixed or nonfixed.

In these experiments, a velocity range of from 13 to 40 feet per second was developed. When the head was allowed to move, higher velocities were required to cause a given injury, than if the head were fixed. An understanding of the physiological effects observed may be aided by a consideration of the mechanical forces involved.

DYNAMICS

The physical forces producing craniocerebral injuries may be grouped into four classes: (1) force applied to a relatively fixed head (direct blow, "compression"); (2) force applied to a nonfixed head which may move by the force (direct blow, "acceleration"); (3) force applied through the head in motion coming in contact with a nonmoving or slower moving object (indirect blow, "deceleration"); (4) a combination of the preceding circumstances.

Whether the head is fixed or allowed to move at the time of the blow and whether certain critical velocities are significant in relation to the morbidity and mortality may be determined by analysis of the experimental data and the underlying physical findings. In this regard, we may consider the question of the forces involved from two points of view; first, that of the work done upon the bone and the intracranial contents; second, the dissipation of momentum at the

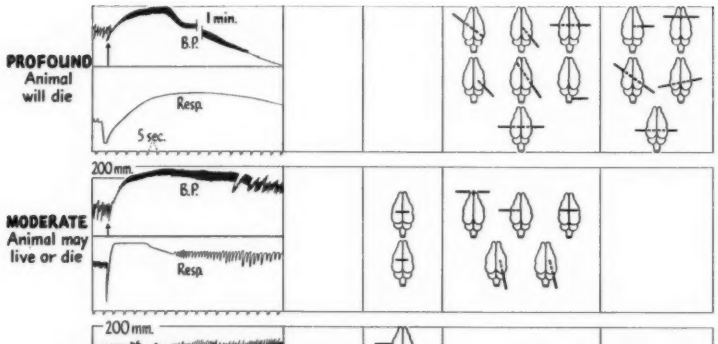

Fig. 8. A correlation of the physiological effect of penetrating and gunshot wounds of the brain, the type of penetration, and the velocity of the injuring object are shown.

instant of injury. In the circumstances of a fixed head, a 5.5 pound weight was allowed to drop from varying heights to the exposed parieto-occipital bone. The object may be considered to be a free falling body. After the weight has made contact with the bone, it is ready to do work upon that bone. The amount of work that it will do is equal to its kinetic energy, a constant quantity for each distance dropped. The head being fixed, the striking object will cause a maximum of work done expressed by damage to the bone and the brain. All the available energy involved is completely dissipated as the weight is stopped by the unmoving head, whereas if the head is allowed to move, part of the energy is dissipated in moving the head.

In the use of a pendulum, whose energies were derived from springs and a vector of the acceleration of gravity, a much greater capacity for work was developed since a greater kinetic energy was available in the instruments. With these devices, the head was allowed to move after being struck. Energy was delivered to the bone and intracranial contents through a longer time interval of contact with the skull. Unlike the conditions of a fixed head, the energy was in part dissipated in moving the nonfixed head. It was dissipated also in the stop bars which were used in the spring and pendulum instruments. It is evident that large velocities were needed in order to parallel the pathological damage obtained by the use of the unobstructed falling weight to the fixed head which did not move the head at striking.

The instrument or hitting object must have a certain quantity of mass before physiological damage may be produced. A relatively great velocity with an extremely small mass may produce minimal injury. Conversely, a large mass with minimal velocity may produce no significant effect. The product of mass and velocity is momentum, a quality which all bodies in motion have. In our experience, the acute physiological and pathological effects of a blow to the head are proportional to the time rate of change of momentum, within an optimum range.

A blow on the head may cause a local effect, a general effect, or a combination of local and general effects. Depending upon the severity of the blow and the dissipation of energy by buffering and deformation, the effect may be local and may result in bruising or laceration of the scalp, fracture or depression of the skull and bruising or laceration of the subjacent brain. If the energy is sufficiently high, it may be transmitted to the contents of the skull, as set forth by Pascal's law. Lesions may be caused in the path of the direction of energy and others may also result in distant portions of the cranial cavity.

The general effects of a blow to the head are brought about by several factors. Among the more important are: first, a sudden intense increased intracranial pressure at the moment of injury; second, mass movements of the brain at the time of the blow; third, cellular damage due to transmitted energy to the head with no accompanying increased intracranial pressure. Any of these factors, or a combination, may result in intracellular, microscopic, or gross disturbance of the intracranial structures.

1. A sudden intense increase in intracranial pressure may occur at the time of the injury and has been demonstrated by Kramer, Cannon, Kocher, and Scott. The increase in intracranial pressure may produce reversible or irreversible cell damage. The most vulnerable cells are involved with ensuing pathophysiological manifestations. The brain stem with its respiratory and vasomotor centers, which are most essential, may become stimulated or inhibited by trauma. Mechanical compression (5), application of electrical currents (17), chemicals and heat (10) to the medulla cause similar stimulation or inhibition of the medullary centers. The conclusions of Scott that the increase in intracranial pressure, lasting $^2/_{10}$ seconds, produces ischemia, that the ischemia in turn results in unconsciousness and hypertension, are not warranted in the presence of strong evidence to show that unconsciousness due to anemia does not occur until 8 to 10 seconds have elapsed (17).

2. Mass movements of the brain may cause microscopic or macroscopic damage. In these observations mass movements occurred with the head fixed or nonfixed. A greater degree of damage occurred due to this cause when the head was nonfixed. Following a blow to the skull, the intracranial contents may abutt against solid structures causing added damage. Similarly, the crowding together of the brain itself because of difference in density may result in parenchymatous lesions. Contrecoup lesions so common in head injury are ascribed to a lag of the brain behind the more rapidly moving cranium or there may be a "bouncing back" of the brain when the moving head is suddenly stopped by a nonmoving or slower moving object. Phenomena of "suction" and "sliding" of the brain have been described in connection with mass movements (23). In our experiments, the presence of contrecoup lesions on the surface of the brain opposite the area of impact suggests that the transmitted energy may travel in a given direction with abuttment of brain against skull at the end of the path of energy (3).

3. Cell derangement may result from the transmitted energy to the skull contents without an increase in intracranial pressure. Energy which injures a brain may produce a "commotio cerebri" (1, 8, 18), "a shaking of the nervous system" (19), "a disturbance of cell equilibrium" (17, 22), "a vulneration of the nerve cells" (12), "a molecular derangement" or "*ebranlement*" (13, 21)—terms used to describe a diffuse response of the intracranial structures at the time of injury. The result of the injury is directly proportional to the intensity of the energy acting upon the head, the result expresses the amount of "work done." Whether the head is fixed or nonfixed at the time of trauma is important in terms of work allowed or degree of dissipation of the momentum. The cellular disturbance may occur from a single application of an adequate quantity of energy or from multiple applications of energy of lesser intensity (21).

The acute physiological effect following a gunshot penetrating wound of the head in the experimental animal may be due, we believe, to the intense, momentary increase in intracranial tension at the instant of injury rather than to "a gradual rise in the intracranial tension due to hemorrhage within the skull cavity" suggested by Kramer and Horsley (16). This phenomenon of increased intracranial pressure was absent in penetration of the brain with a low velocity object. The force, known as "explosive force," of a high velocity bullet transmitted to a closed, semifluid system, resulting in a sudden, increased, intracranial pressure, is dispersed throughout; acts upon all tissue; is manifested by the response of the vital medullary centers. Vital cell or center injury, recoverable or fatal, may be the direct result of this sudden pressure. The indirect effects of intrinsic vascular damage plus the local destructive process may cause additional immediate or delayed injury to the cells. Mention only is necessary to indicate that injuries by extensive dissolution of the brain as well as those produced by extreme velocities were excluded from this study.

In summary, trauma to the head causes acute pathophysiological effects through visible and invisible damage to the intracranial structures in a manner outlined. Other known and unknown factors act in the interval between the application of the force and the recovery or death of the subject. Known factors include immediate or secondary vascular damage, hemorrhage, infection, gross tissue destruction by macerating low velocity objects or shattering high velocity shell fragments or bullets.

Unknown factors include chemical and physicochemical processes which occur following trauma. Only meager efforts have been directed toward this line of investigation. Outstanding among these is the work of Cannon who studied the later or secondary effects of injuries and arrayed evidence to show that the forces of osmosis play a significant rôle in cell injury. It is reasonable to believe that factors of this order deserve recognition in the development of a full view of the subject of brain injury. This phase has not been included in the sphere of our present observations.

SUMMARY

1. Cranial trauma was produced in 150 morphinized dogs under controlled conditions by varying the type and intensity of the injuring forces.

2. A correlation was observed between the intensity of the injuring force or the "work done" upon the skull and brain and the physiological and pathological effects of injury.

3. A correlation was also found to exist between the physiological effect of injury and the degree of gross pathological changes produced. Death was not observed to occur without visible pathological damage being produced in the brain.

4. A remarkable, sudden increase in blood pressure was usually noted in the moderate and profound classes of injuries. This phenomenon was often accompanied by loss of the palpebral and corneal reflexes, loss of respirations, and unconsciousness lasting for varying periods. Recovery or death occurred in the moderate, while death always occurred in the profound group of injuries.

5. Animals were observed to be unconscious with active palpebral and corneal reflexes. Loss of these reflexes represented a more profound response to injury than loss of consciousness.

6. Penetrating gunshot injuries of the brain resulted in acute physiological effects similar to those which were noted in other forms of trauma.

7. Injuries were produced to the nonfixed head with striking objects propelled by a spring, pendulum, and hammer within a range of velocity from 13 to 40 feet per second. Higher velocities were required to produce pathophysiological effects under the circumstances of the nonfixed head than the fixed head. Whether the head was fixed or nonfixed at the time of injury was important to the extent of the "work allowed" upon the skull and contents, that is, at a given velocity the pathological and physiological damage was less marked if the head were allowed to move. However, a greater degree of mass movements of the brain may occur under conditions of a nonfixed head.

8. The total acute effect of cranial trauma is due to a number of factors which includes: (1) a sudden intense increase in intracranial pressure at the instant of injury; (2) mass movements of the brain; (3) a diffuse cellular disturbance due to transmitted energy with no accompanying increased intracranial pressure.

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EDITORIALS

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MAY, 1943

BACTERIA AND THE SURGEON

SURGEONS are constantly encountering problems of sepsis, asepsis, and antisepsis. In spite of this fact, there are too many surgeons who know too little about bacteria and their habits. Frequently they take cultures from wounds or exudates but pay little or no attention to even the laboratory report of the findings, let alone making any practical use of it. Too often, they regard the bacteriologic problem as being an academic one, apart from the clinical aspects of the case, something for the laboratory technician to work out, and for the hospital superintendent to report in the analysis of cases. This, of course, is not true, for the whole science and art of surgery depends so greatly on bacteriology. Without asepsis, practically the whole field of elective surgery would collapse. The intelligent care of infected wounds demands a thorough knowledge of bacteria, how they grow or how they may be inhibited. Who is in a better position to make contributions in this field than the surgeon who sees and dresses the wound, or who opens and drains the abscess, and follows the clinical progress of the patient? Certainly not the laboratory technician or the bacteriologist whose chief interest is often concerned with the staining reactions of the organism, its reaction to culture media, to oxygen tension, and other similar qualities which allow it to be diagnosed and classified.

It is well known that many of the problems in surgical bacteriology have been solved by surgeons who are also trained bacteriologists. To mention only a few, one immediately thinks of the sterilization and standardization of catgut, the use of zinc peroxide by Meleney in the treatment of certain types of burrowing, progressive ulcerative lesions, and the use of high titered bacteriophage in the treatment of staphylococcus septicemia. Many studies on such matters as tetanus and gas bacillus infections have been made and are still being made by surgeon bacteriologists.

During the past few years, the development of the sulfone compounds and their use locally and systemically have further demoralized many surgeons, who now believe that throwing some of the "magic powder" into wounds and body cavities relieves them of further responsibilities, and if infection then develops or persists it is a sad trick of fate and no fault of theirs. Nothing could be farther from the truth. Many wounds heal more kindly without these drugs if adequate care and toilet of the wound are carried out. In this war, as in the last one, great emphasis has been placed on the healing of traumatic wounds and the best way to manage them. While many an average surgeon believes that he knows the best way, many experts are not so satisfied

that they do. They are studying with great care the results of various methods, with and without débridement, with and without closure, with and without sulfone compounds, etc. Careful cultural studies of tissue obtained by débridement, such as those made by Altemeier, throw considerable light on the subject and value of this procedure. Discussion with many surgeons by the writer has convinced him that débridement is employed very differently by different operators and that what one man regards as a careful and thorough débridement would be considered as inadequate by another. The problem of the management of traumatic wounds including burns, still has to be considered as an incompletely solved problem, for while these lesions today are treated better than they have been in the past, one has only to look at the multiplicity of methods advocated to realize that the ideal treatment has not been achieved. There is, therefore, still ample opportunity to make contributions in this field of medicine, and the surgeon who is willing to make use of the existing bacteriologic knowledge in his care of wounds, should be in the best position to help in solving this problem.

M. M. ZINNINGER.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

ALL of the contributors to the first edition of Morris' *Human Anatomy*[1] were Englishmen, associated with hospitals in or near London. The volume was originally designed for the use of students "preparing for the Conjoint Board of the Royal Colleges of Physicians and Surgeons, for the Fellowship of the Royal College of Surgeons," etc. The contributors to the current 10th edition are 12 Americans, who hold, or have held, professorial appointments in anatomy, in medical schools of the United States or Canada; no one of the original authors of the work, first published almost 50 years ago, is on the present list.

Editorship of the present edition was assumed by Professor Schaeffer after ill health required Professor Jackson to withdraw from such duty. As the editor's preface records, death has removed Professors Bardeen, Senior, and Stockard from the list of contributors, while Professor Hardesty has retired from activity associated with the new edition. These earlier contributors have been replaced by Professors Grant, Patten, Cummins, and Larsell, in the preparation of the sections on the musculature, the cardiovascular system, the skin (and special glands), and the nervous sytem, respectively.

Several sections of the treatise have been profoundly altered in rewriting, others have been rather moderately changed. Many of the older, inadequate figures have been replaced, chiefly by borrowing extensively from impeccable foreign sources. The sectional lists of important bibliographic references have been extended, an improvement which should be welcomed by all teachers and advanced students of gross anatomy.

The first section, on developmental anatomy, while actually shorter than it was in the prior edition, is nevertheless far more informative, since descriptive material has been converted into series of schematic figures. Professor Scammon has made each set self-contained and, through ingenious labeling, virtually self-explanatory. By this means the general developmental history of viscera, skeleton, and nervous system, to name but several items, is managed graphically. The 2d section, dealing with the skin and its modifications, has been rewritten by Professor Cummins, with additions to text and illustrations. The 3d and 4th sections, on osteology and articulations, by Professor Terry, have been made more readable through being set up in regular type; the use of fine print has been reduced to a minimum. In the form revised by Professor Grant, the 5th section, on musculature, has been slightly lengthened; major descriptive material on origin, form, course, and insertion of muscles is set up in regular type, an arrangement convenient to the student who must read his book at the dissection-table; descriptions of action, relations, and variations are in fine print. In general the subject matter is fortunately presented in the critical form composed by the late Professor Bardeen. The 6th section, on the cardiovascular system, enlarged by Professor Patten, retains much of the textual substance of its predecessors, but is greatly improved by the new account of morphogenesis and variations of the vascular system which is illustrated by diagrammatic figures. Many new colored figures have been added, borrowed from the Tandler *Lehrbuch*. The 7th section, dealing with the lymphatic system, by Professor Clark, remains essentially the same, as does section IX on the special sense organs by Professor Arey. These chapters, thoroughly revised for the earlier edition, required little alteration. In the 8th section rewritten by Professor Larsell, is contained the bulk of the neural material presented in earlier editions but modernized through additional detailed descriptions on nuclear masses and tracts, and accompanying diagrams. The 9th section by Professors Jackson and Blount contains numerous new and helpful illustrations, and the older ones are improved. The text contains concise accounts of recent researches, affecting, among other areas, the gall bladder and biliary ducts. These statements also apply, generally, to the 11th section on the respiratory system, by Professor Schaeffer, and to section XII, by Professor Johnson, on the urogenital system. In the 13th section, by Professor Gudernatsch, on the anatomy of the glands of internal secretion, new figures have been added and the text has been brought up to date.

The volume is about 100 pages longer than it was in the prior edition, but the added bulk has been most advantageously used. The descriptive material has been printed in type of easily readable size. The work continues to be encyclopedic, in the traditional manner; it contains, to approximately one-sixth of its bulk, material that is nowadays handled admirably by the separate textbooks of embryology, neurology, and histology. BARRY ANSON.

THE ever-increasing incidence of malignant disease throughout the civilized world and the equally increasing occurrence of hazards of industrial life as well as those associated with the average trend of modern living, many apparent and controlled and many not, suggest a study of a possible relationship. Studies have been made of carcinogenetic sub-

[1] MORRIS' HUMAN ANATOMY; A COMPLETE SYSTEMATIC TREATISE. Edited by J. Parsons Schaeffer, A.M., M.D., Ph.D., Sc.D. 10th ed. Philadelphia: The Blakiston Co., 1942.

stances, their structure determined, and their occurrence in matter that may come in contact with the human body established. Also many apparently benign substances have been studied with the view of determining the presence of carcinogens. Many of these reports are inaccessible and appear in scattered journals throughout the world. To answer this pertinent problem a compilation of factual information on the subject of tumors of occupational origin has been prepared by Hueper.[1]

The casual student of the subject cannot realize the enormous amount of work that has been done on the problem. The average physician, as an example, is aware of tar as a causative agent in the production of experimental cancer; however, he has not the slightest conception of the tremendous amount of study that has been given the subject. This is well exemplified in this new work. Here under tumors of the skin the author considers of the organic chemicals "the distillation and fractionation of coal, oil shale, lignite, bitumen, goudron, asphalt, crude mineral oil, and similar naturally occurring substances." To this is devoted some 120 pages. Such detail as distribution, chemical and technological aspects, historical and geographical aspects, exposure and incidence, symptomology, site, multiplicity, prognosis, age, duration of exposure, sex, constitution, latency period, acute traumatic tar cancer, histopathology, experimental tar and pitch cancer, causative mechanism, and technical, sanitary, and medical protective aspects are considered. For those interested in these substances the low and high temperature distillations ranging from 105 to 300 degrees C are discussed.

Chapters are devoted to concepts and significance of occupational tumors, occupational and accidental tumors of the skin and its appendages, the alimentary system, respiratory system, the urogenous organs, hyperplasia and neoplastic diseases of the blood-forming organs, tumors of the mesenchymatous tissue, the eye and its adnexa, the nervous system, the endocrine glands, the sex organs, special aspects of occupational tumors, the relationship of occupational neoplasia to the theories of cancerigenesis and medicolegal and public health aspects.

This work contains such an enormous amount of information that it is beyond the scope of a review to describe the contents. It is fascinating reading for one interested in the subject of tumors or industrial hazards. Because of the pathological associations, more is included than the problem of neoplasia. In the chapter devoted to the alimentary system can be found an extremely interesting survey of cirrhosis of the liver. The chapter on the respiratory system is timely and pertinent in view of the fact that cancer of the lung has become so prevalent during the past decade or two. The same comment may be made on the chapter on the urogenous system because of the impression that bladder carcinoma is definitely increasing. At the conclusion of each chapter is appended an extensive bibliography.

[1]Occupational Tumors and Allied Diseases. By W. C. Hueper, M.D. Springfield, Ill., and Baltimore, Md.: Charles C. Thomas, 1942.

There has been accomplished the aim expressed by the author in the preface: "It is the principle aim of this book to furnish an extensive source of information concerning the various aspects and the different types of these neoplastic disorders which have come to claim an ever-increasing importance as a part of the problem of cancer in general. A reference book is now offered in which the pertinent data, often not readily accessible and widely scattered in journals, have been compiled. An attempt is made to analyze critically and to integrate the evidence obtained from different sources, and to correlate and evaluate the various observations and theoretical conceptions advanced, so as to form a well balanced and, when possible, coherent picture of the subject under discussion."

This work should be of special value to every physician, to governmental and legislative groups dealing with public health problems, and to the industrial employers. The author must be congratulated upon the completion of such an enormous task and his sane evaluation of the compiled data.

John A. Wolfer.

THE 13th edition of *Physical Diagnosis* by Richard C. Cabot and F. Dennette Adams[2] scarcely needs introduction to most students of medicine, as this volume has been used throughout most of its editions as a standard text.

Adams collaborated in a complete revision of this book in the 12th edition. The present edition has again been extensively re-edited. The volume is much larger and more complete than earlier editions. It contains a text of 833 pages with a full and detailed index of 53 pages.

The material presented is primarily the teaching views and standards of the medical history and physical diagnosis upheld by the staff of the Massachusetts General Hospital. In addition accepted clinical procedures presented in the current literature are given.

The purpose of the book has been expressed by the author in the preface as follows: "To show how we think the patient should be examined, to describe and interpret important symptoms and signs, and briefly to discuss the more common disorders in which they occur." Strict adherence to this policy, makes the volume useful as a reference text of differential diagnosis.

A criticism concerning the propriety of including discussions of clinical entities in a basic book of physical diagnosis has been capably answered in the preface. The author states: "I can only emphasize again, my conviction on which the 12th edition was based, that physical signs can be intelligently taught and intelligently learned only in their relationship to, and not apart from the other aspects of disease." If this concept is borne in mind, certainly the approach and plan of the text are fundamentally sound.

[2]Physical Diagnosis. By Cabot and Adams. 13th ed. by F. Dennette Adams, M.D. Baltimore: The Williams & Wilkins Co., 1942.

The section on cardiovascular disease follows the Massachusetts General Hospital etiological classification, which the author admits is incomplete. It is unfortunate that the classification of cardiac disorders of the American Heart Association has not been included, or at least, presented for discussion.

The format of the book, as in previous editions, is excellent. The plan of presenting the subject by anatomic systems of necessity involves repetition of certain disease entities in the discussion. This, however, is effective and well tolerated by the reader.

I believe this volume will be found more practical than previous editions, not only for medical graduates, but also for the student just beginning his studies in clinical medicine. EUGENE L. WALSH.

BECAUSE of its general plan, the broad field covered, and the excellence of the individual papers the 3d volume of the *Medical Progress Annual*[1] should be of interest to every clinician. It serves as an admirable "Year Book" of value not only to the specialist but also to general practitioners, internes, and to 3d and 4th year medical students.

The book consists of 52 articles that have been reprinted from issues of the *New England Journal of Medicine* for 1941. These articles represent the efforts of well qualified writers to cover recent advances in diagnosis and treatment in various fields, either in a general way or as they apply to some particular aspect of the specialty. The improvements in medical practice that, in the opinion of the authors, have been accepted and should be utilized are stressed. The list of references at the end of each article should be particularly helpful. A subject index is provided. Subjects of special interest to surgeons include general anesthesia, diagnostic roentgenology, operative technique, shock, transfusion reactions, surgery of the abdomen and of the sympathetic nervous system, thoracic and neurosurgery, radiation therapy in gynecology, treatment of pneumonia and of biliary tract disease. WALTER H. NADLER.

THOUGH in the title of *A Short History of Cardiology*[2] by Herrick the word "short" is used the outstanding and essential developments in the knowledge of the heart since the time of Harvey (1628) are adequately described in the volume. A short chapter, introductory in character, is given to the scant knowledge of the heart prior to the time of Harvey; Hippocrates, Galen, and Vesalius with a short notice of Leonardo da Vinci, whose interest was confined to anatomy, are discussed in the first chapter. Three chapters entitled "Harvey to Laennec," "Laennec to Virchow," and "Virchow to Pasteur" make up the most of the book. Shorter chapters entitled "Inflammation of the Heart," "Affections of the Myocardium," "Syphilis of the Heart and Aorta," and "The Coronary Artery and its Diseases" make up the rest of the book.

The author has presented a comprehensive and interesting story of the gradual development of our knowledge of cardiac disease. While presenting the history of research in cardiac disease, the author portrays the characters of many physicians from many lands, whose pioneer work is presented. Dr. Herrick has a gift for appraising his characters concisely and accurately; the facts of scientific investigation are made more interesting in the light thrown upon them by one who belongs to the inner circle of medical research. The author found time to portray the characters of the more important investigators; he tells not of science alone but of personalities. He has described the various approaches to research in times of ignorance and the tenacity which most of the investigators needed to maintain their discoveries. For instance, he gives some 15 pages to Bouillard, whose thorough work resulted in the demonstration of the relationship of acute rheumatic fever to cardiac disease.

The book is adequately bound and well printed. It will delight the members of our profession who are especially interested in cardiac disease; it will intrigue the physicians who are interested in medical history; the descriptions of the clinical studies and investigative procedures in widely different times may be read with pleasure and profit by the medical profession but also by many from every walk of life who are interested in the history of science as well as medicine. JAMES G. CARR.

ANY writer who undertakes the herculean task of compressing into a single volume the enormous body of knowledge connoted by the title *Human Pathology*[3] deserves respectful consideration, even though complete success is impossible. Dr. Karsner acknowledges the book's limitations when he says in his preface to the first edition: "A textbook is only an introduction to the essentials of a subject." The book has been popular as the appearance of 6 editions in 16 years well demonstrates. The material is presented in the pattern generally accepted as best designed for the instruction of medical students, dealing first with general topics and later taking up systemic pathology. In this latter division the author demonstrates the breadth of his knowledge by including many topics of interest to surgeons which are slighted or omitted in several other well known textbooks on the subject. The present edition contains much recent material and new references so that one can rest assured that revision has been painstaking and judicious.

There are omissions which are common to most textbooks of general pathology. There are, for example, no chapters devoted to the eye, the ear, and the skin. Perhaps this can be justified for the eye and ear, but the skin must be reckoned with by almost every physician, and surely some familiarity

[1] MEDICAL PROGRESS ANNUAL. VOL. 3, 1942. A SERIES OF FIFTY-TWO REPORTS ON THE RECENT ACCEPTED ADVANCES IN DIAGNOSIS AND TREATMENT. Published during 1941 in The New England Journal of Medicine. Robert M. Nye, Managing Editor. Springfield, Ill., and Baltimore, Md.: Charles C. Thomas, 1942.

[2] A SHORT HISTORY OF CARDIOLOGY. By James B. Herrick. Springfield, Ill., and Baltimore, Md.: Charles C. Thomas, 1942.

[3] HUMAN PATHOLOGY. By Howard T. Karsner, M.D. 6th ed. Philadelphia, Montreal, and London: J. B. Lippincott Co., 1942.

with its pathology is essential for intelligent practice. The question of emphasis and space allotment will not meet with universal agreement; inevitably it could not do so for each one of us has varying ideas about which are the more important lesions. On the whole, Dr. Karsner has done a good job, and where lesions are only mentioned and not described, judiciously selected references enable one to seek more detailed information.

The illustrations are clear and usually illuminate the text instead of obscuring it, as is the case in some books. The type is good and easy to read and references are up to date. An incomplete index, which delays one in finding some topics, is the only mechanical defect to be found in an otherwise carefully prepared text.

This textbook can be recommended to medical students as one of the best single volume general pathologies. For graduates in medicine it will be useful as a book of reference and for its bibliography. The surgeon will need more detailed knowledge of the pathology of the diseases which he treats to supplement the information contained in this volume.

ARTHUR PURDY STOUT.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

I SERVED ON BATAAN. By Juanita Redmond, A.N.C. Philadelphia and New York: J. B. Lippincott Co., 1943.

THE PRINCIPLES AND PRACTICE OF OBSTETRICS. By Joseph B. DeLee, A.M., M.D., and J. P. Greenhill, B.S., M.D. 8th ed. Philadelphia and London: W. B. Saunders Co., 1943.

BURNS, SHOCK, WOUND HEALING AND VASCULAR INJURIES. Prepared under the auspices of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Philadelphia and London: W. B. Saunders Co., 1943.

ILLUSTRATIONS OF SURGICAL TREATMENT; INSTRUMENTS AND APPLIANCES. By Eric L. Farquharson, M.D., F.R.C.S.E., Major R.A.M.C., with a foreword by Sir John Fraser, (M.C.), M.D., Ch.M., F.R.C.S.E. 2d ed. Baltimore: The Williams & Wilkins Co., 1942.

OBSTETRICAL PRACTICE. By Alfred C. Beck, M.D., 3d ed. Baltimore: The Williams & Wilkins Co., 1942.

DISEASES OF THE NOSE, THROAT AND EAR; MEDICAL AND SURGICAL. By William Lincoln Ballenger, M.D., F.A.C.S., and Howard Charles Ballenger, M.D., F.A.C.S. 8th ed. Philadelphia: Lea & Febiger, 1943.

MAN IN STRUCTURE AND FUNCTION. By Fritz Kahn. Translated from the German and edited by George Rosen, M.D. 2 vols. New York: Alfred A. Knopf, 1943.

THE PRINCIPLES AND PRACTICE OF WAR SURGERY; WITH REFERENCE TO THE BIOLOGICAL METHOD OF THE TREATMENT OF WAR WOUNDS AND FRACTURES. By J. Trueta, M.D., with introduction by Owen H. Wangensteen, M.D. St. Louis: The C. V. Mosby Co., 1943.

ESSENTIALS OF PROCTOLOGY. By Harry E. Bacon, B.S., M.D., F.A.C.S., F.A.P.S., with an introduction by Curtice Rosser, B.A., M.D., F.A.C.S., F.A.P.S. Philadelphia, London, Montreal, J. B. Lippincott Co., 1943.

PANCREATITIS AGUDA; APOPLEJIA DEL PANCREAS-ABDOMEN AGUDO PSEUDO-QUISTE DE PANCREAS PERITONITIS BILIAR SIN PERFORACION. By Alfonso R. Albanese. Buenos Aires: Nocita & Rañó, 1942.

OPERATING ROOM TECHNIQUE. By Edythe Louise Alexander, R.N. St. Louis: The C. V. Mosby Co., 1943.

BEHIND THE SULFA DRUGS; A SHORT HISTORY OF CHEMOTHERAPY. By Iago Galdston, M.D., with a preface by Perrin H. Long, M.D. New York and London: D. Appleton-Century Co., 1943.

GYNECOLOGY; WITH A SECTION ON FEMALE UROLOGY. By Lawrence R. Wharton, Ph.B., M.D. Philadelphia and London: W. B. Saunders Co., 1943.

NEUROSURGERY AND THORACIC SURGERY. Prepared and edited by the Subcommittee on Neuro-surgery and Thoracic Surgery of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Philadelphia and London: W. B. Saunders Co., 1943.

SYNOPSIS OF DISEASES OF THE SKIN. By Richard L. Sutton, M.D., and Richard L. Sutton, Jr., M.D. St. Louis: The C. V. Mosby Co., 1942.

DOCTOR IN THE MAKING; THE ART OF BEING A MEDICAL STUDENT. By Arthur W. Ham, M.B., and M. D. Salter, M.A., Ph.D. Philadelphia, London, Montreal; J. B. Lippincott Co., 1943.

NURSES IN ACTION; THE STORY OF THE ARMY NURSE CORPS. By Colonel Julia O. Flikke, A.U.S., with an introduction by Lt. Col. L. L. Gardner, M.C., A.U.S. Philadelphia, New York, and London: J. B. Lippincott Co., 1943.